*Current Policy Effective Date: 11/1/22
(See policy history boxes for previous effective dates)

Title: Ultrasonographic Measurement of Carotid Intima-Media Thickness as an Assessment of Subclinical Atherosclerosis

Description/Background

CORONARY HEART DISEASE

Heart disease is the leading cause of mortality in the United States, accounting for more than half of all deaths. Coronary heart disease (CHD), also known as coronary artery disease, is the most common cause of heart disease.[1] In a 2022 update on heart disease and stroke statistics from the American Heart Association, it was estimated that 720,000 Americans have a new coronary attack (first hospitalized myocardial infarction or CHD death) and 335,000 have a recurrent attack annually. An estimated 20.1 million Americans ≥20 years of age have CHD. The prevalence of CHD was higher for males than females ≥60 years of age. Total CHD prevalence is 7.2% in US adults ≥20 years of age; CHD prevalence is 8.3% for males and 6.2% for females. On the basis of data from the 2018 National Health Interview Survey, CHD prevalence estimates are 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people ≥18 years of age.

Established major risk factors for CHD have been identified by the National Cholesterol Education Program Expert Panel. These risk factors include elevated serum levels of low-density lipoprotein cholesterol and 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.

Diagnosis

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 2 or more risk factors for more intensive lipid management.[2] 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 an 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 atherosclerosis. B-mode ultrasound is most commonly used to measure the CIMT. Carotid intima-media thickness 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 CIMT measurements than imaging the near wall. Two echogenic lines are produced, representing the lumen-intima interface and the media-adventitia interface. The distance between these 2 lines constitutes the CIMT.

Regulatory Status:

In 2003, SonoCalc® (SonoSite) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA determined that this software was substantially equivalent to existing image display products for use in the automatic measurement of the intima-media thickness of the carotid artery from images obtained from ultrasound systems. Subsequently, other devices have been cleared for marketing by FDA through the 510(k) process.
Product code LLZ.

Medical Policy Statement

Ultrasonographic measurement of carotid artery intima-media thickness to screen, diagnose or manage subclinical atherosclerosis is considered experimental/investigational. Although it may be safe, its usefulness has not been definitively proven.

Inclusionary and Exclusionary Guidelines **(Clinically based guidelines that may support individual consideration and pre-authorization decisions)**

N/A

CPT/HCPCS Level II Codes ***(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)***

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

93895 93998

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

ULTRASONOGRAPHIC MEASUREMENT OF CAROTID IMTIMA-MEDIA THICKNESS

Clinical Context and Test Purpose

The purpose of ultrasonographic measurement of carotid intima-media thickness (CIMT) is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as standard of care and alternative cardiovascular (CV) risk predictors, in patients who are undergoing cardiac risk assessment.

The question addressed in this evidence review is: Do the results of ultrasonographic measurement of CIMT improve risk categorization in individuals who are undergoing cardiac risk assessment?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are undergoing cardiac risk assessment. This population may have other risk factors for coronary heart disease (CHD), including a history of cigarette smoking, hypertension, family history of premature CHD, and age.

Interventions

The test being considered is ultrasonographic measurement of CIMT. Ultrasonographic measurement of CIMT refers to the use of B-mode ultrasound to determine the thickness of the 2 innermost layers of the carotid artery wall, the intima and the media. Detection and monitoring of intima-medial thickening, which is a surrogate marker for atherosclerosis, may provide an opportunity to intervene earlier in atherogenic disease and/or monitor disease progression.

Comparators
Comparators of interest include the standard of care and alternative CV risk predictors.

Standard of care includes hypertension/blood pressure control and regular screenings. Alternative CV risk predictors commonly refer to the Framingham Risk Score, a gender-specific algorithm used to estimate the 10-year CV risk of an individual. The Framingham Risk Score was first developed based on data obtained from the Framingham Heart Study, to estimate the 10-year risk of developing CHD. In order to assess the 10-year cardiovascular disease (CVD) risk, cerebrovascular events, peripheral artery disease and heart failure were subsequently added as disease outcomes for the 2008 Framingham Risk Score, on top of CHD.

Outcomes
The general outcomes of interest are test accuracy and morbid events. Possible negative outcomes include stroke, myocardial infarction (MI) and heart failure.

Table 1. Outcomes of Interest for Individuals Who are Undergoing Cardiac Risk Assessment

Outcomes	Details	Timing
Test accuracy	Evaluating the efficacy of CIMT in assisting in the estimation of the risk of CVD using tools such as the Framingham Risk Score or the European systematic coronary risk evaluation	1-10 years
Morbid events	Cardiovascular events (eg, MI, stroke, angina, vascular death)	5-10 years

CIMT: carotid intima-media thickness; ; CVD: cardiovascular disease; MI: myocardial infarction.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.
- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

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).

REVIEW OF EVIDENCE

Systematic reviews
Mookadam et al (2010) conducted a systematic review of the role of CIMT in predicting individual CV event risk and as a tool in assessing therapeutic interventions.[3] Reviewers

concluded that CIMT is an independent risk factor for CV events and may be useful in determining treatment when there is uncertainty regarding the approach or patient reluctance. However, further studies are needed to identify the best approaches to screening and interventions to prevent the progression of atherosclerosis.

In a meta-analysis, the USE Intima-Media Thickness collaboration, investigators sought to determine whether common CIMT measurements can assist in estimating the 10-year risk of first-time myocardial infarction (MI) or first-time stroke when added to the Framingham Risk Score.[4] Den Ruijter et al (2012), using individual data for 45,828 patients from 14 population-based cohort studies, found that the risk of first-time MI or stroke was related positively to both the Framingham Risk Score and the adjusted common CIMT. The mean common CIMT was 0.73 mm, and it increased in every cohort with patient age during a median follow-up of 11 years. For every 0.1 mm difference in common CIMT, the hazard ratio (HR) for risk of MI or stroke, which occurred in 4007 patients, was 1.12 (95% confidence interval [CI], 1.09 to 1.14) for women and 1.08 (95% CI, 1.05 to 1.11) for men. However, adding common CIMT measurements to the Framingham Risk Score did not improve risk prediction and resulted in the reclassification of risk in only 6.6% of patients. The added value of mean common CIMT in reclassifying risk was only 0.8% (95% CI, 0.1% to 1.6%) and did not differ between men and women. The C statistic of the Framingham Risk Score model with and without CIMT was similar for men (0.759; 95% CI, 0.752-0.766) and women (0.757; 95% CI, 0.749 to 0.764), suggesting the addition of CIMT in risk assessment offered limited benefit.

Lorenz et al (2012), in another meta-analysis, pooled individual participant data from 16 studies (N=36,984), and examined CIMT progression from 2 ultrasound screenings taken 2 to 7 years apart (median, 4 years).[5] Patients were followed for a mean of 7 years, during which time 1339 strokes, 1519 MIs, and 2028 combined end points (MI, stroke, vascular death) occurred. The mean CIMT of the 2 ultrasound results was predictive of CV risk using the combined end point (adjusted HR, 1.16; 95% CI, 1.10 to 1.22). In sensitivity analyses, no associations were found between CV risk and individual CIMT progression regardless of CIMT definition, end point, and adjustments. As an example, for the combined end points, an increase of 1 standard deviation in mean common CIMT progression resulted in an overall estimated HR of 0.97 (95% CI, 0.94 to 1.00) when adjusted for age, sex, and mean common CIMT; the HR was 0.98 (95% CI, 0.95 to 1.01) when adjusted for vascular risk factors. These data confirmed that CIMT is a predictor of CV risk but did not demonstrate that changes in CIMT over time are predictive of future events.

Van den Oord et al (2013) published a meta-analysis of 15 articles by and found similar results on the added value of CIMT.[6] Six cohort studies (N=32,299) were evaluated to examine the predictive value of CIMT when added to traditional CV risk factors. Although a CIMT increase of 0.1 mm was predictive for MI (HR, 1.15; 95% CI, 1.12 to 1.18) and stroke (HR, 1.17; 95% CI, 1.15 to 1.21), the addition of CIMT did not statistically increase risk prediction over traditional CV risk factors (p=.8).

Bytyçi et al (2021) 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 ≥ 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.

Tschiderer et al (2020) published a meta-analysis of 7 prospective studies examining the extent to which CIMT predicts the incidence of carotid plaque in individuals free of carotid plaque at baseline.[8] Results showed that when individuals in the top fourth of baseline CIMT distribution were compared with those in the bottom fourth, the relative risk for incidence of first-ever carotid plaque was 1.78 (95% CI, 1.53 to 2.07; p<.001).

Studies have found including carotid plaques in CIMT increases the predictive value of CV risk over CIMT assessed only in plaque-free sites.[9,10,11,12] However, Lorenz et al (2012) found no difference in the main results between studies that included CIMT with carotid plaque and plaque-free CIMT.[5] Peters et al (2012) found in their systematic review that adding carotid plaque to the traditional CIMT model increased the C statistic from 0.01 to 0.06.[13]

Table 2. Systematic Reviews & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Lorenz et al (2012)[5]	NR	16	Patients who were assessed with CIMT at least twice and followed up for MI, stroke, or death	36,984 (297 to 12,221)	Prospective, longitudinal, observational	NR
van den Oord et al (2013)[6]	1997-2011	15	Patients at risk for CV events	76,201 (1,734 to 14,214)	Observational studies	NR
Tschiderer et al (2020)[8]	Through October 2019	7	Patients free of carotid plaque at baseline	9,341	Prospective studies	mean, 8.7y (range, 2 to 12 y)
Bytyçi et al (2021)[7]	Through September 2020	89	Patients with suspected or confirmed CAD	22,683	4 clinical trials; 85 observational studies	NR

CAD: coronary artery disease; CIMT: carotid intima-media thickness; CV: cardiovascular; MI: myocardial infarction; NR: not reported

Table 3. Systematic Reviews & Meta-Analysis Results

Study	**CIMT Progression** HR (95% CI)	**Association of CIMT with CV Risk** HR (95% CI)
Lorenz et al (2012)[5]	0.97[a] (0.94 to 1.00)	1.16 (1.10 to 1.22)
		Association of 1 SD (0.1 mm) Increase in CIMT With Future MI HR (95% CI)
van den Oord et al (2013)[6]	NR	1.26 (1.20 to -1.31)
		Association of top vs bottom fourth of baseline CIMT with first-ever carotid plaque RR (95% CI)
Tschiderer et al (2020)[8]		1.78 (1.53 to 2.07)
		Association of CIMT with CAD WMD (95% CI)

Bytyçi et al (2021)[7]		-0.18 (-0.16 to -0.21)

CAD: coronary artery disease; CI: confidence interval; CIMT: carotid intima-media thickness; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; NR: not reported; RR: relative risk; SD: standard deviation; WMD: weighted mean difference.
[a]When adjusted for age, sex, and mean common CIMT.

Prospective Cohort Studies

Numerous prospective cohort studies have evaluated the association between CIMT and future CV events. Some of the larger trials are discussed below. For example, in the Atherosclerosis Risk in Communities study, trialists evaluated risk factors associated with increased CIMT in 15,800 subjects.[14] Carotid intima-media thickness had a graded relation with increasing quartiles of plasma total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Carotid intima-media thickness also correlated with the incidence of CHD in a subgroup of patients enrolled in the trial after 4 to 7 years of follow-up.[15] Among the 12,841 subjects studied, there were 290 incident events. The HR rates for women and men, adjusted for age and sex, comparing extreme CIMT (ie, ≥1 mm) with nonextreme CIMT (ie, <1 mm), were 5.07 for women and 1.85 for men. The strength of the relation was reduced by including major CHD risk factors but remained elevated for higher measurements of CIMT. The authors concluded that mean CIMT was a noninvasive predictor of future CHD incidence.

The Rotterdam cohort study started in 1989 and recruited 7983 men and women aged 55 years and older.[16] Its main objective was to investigate the prevalence and incidence of risk factors for chronic diseases, including cardiovascular disease (CVD), in older adults. One aspect of the study sought to determine whether the progression of atherosclerosis in asymptomatic elderly subjects is a prelude to CV events. Measurements of CIMT were used to assess the progression of atherosclerosis. Increasing CIMT was associated with increasing risks of stroke and MI.

O'Leary et al (1999) performed CIMT in 4476 asymptomatic subjects aged 65 years or older without clinical CVD in the Cardiovascular Health Study.[17] The incidence of CV events correlated with measurements of CIMT; this association remained significant after adjustment for traditional risk factors. The authors concluded that increases in CIMT are directly associated with an increased risk of MI and stroke in older adults without a history of CVD.

The longitudinal Carotid Atherosclerosis Progression Study included 4904 subjects. All subjects received a baseline CIMT measurement as well as traditional risk factor analysis and were followed for 10 years (mean follow-up, 8.5 years; range, 7.1 to 10.0 years). Adverse events were MI in 73 (1.5%) patients, angina or MI in 271 (5.5%) patients, and death in 72 (1.5%) patients. Lorenz et al (2010) retrospectively reviewed Carotid Atherosclerosis Progression Study data.[18] They modeled the predictive value of CIMT on adverse events within that decade. Because the thresholds of CIMT measurements that would lead to reclassification of risk are unknown, the authors used 24 models of reclassification and 5 statistical tests. Each model compared the predictive value of traditional risk factors alone with those risk factors plus CIMT. None of the reclassification models improved with the addition of CIMT measurements. Investigators concluded that their retrospective analysis did not support the use of CIMT as a clinically useful risk classification tool when used with traditional risk factor analysis.

In the Multi-Ethnic Study of Atherosclerosis (MESA) trial, an ongoing cohort study of atherosclerosis, CIMT was found to be a modestly better predictor of stroke, but it was a worse predictor of CHD than coronary artery calcium (CAC) score at a median follow-up of 3.9 years among 6698 adults asymptomatic at baseline.[19] Paramsothy et al (2010), also reporting on the MESA trial, compared CIMT results in 4792 healthy individuals (nondiabetic adults not on lipid-lowering medications) across 6 different lipid groups, including normolipemia and several types of common dyslipidemias.[20] Mean CIMT values were increased only for the combined hyperlipidemia (defined as any high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol ≥160 mg/dL, and triglyceride ≥150 mg/dL) and simple hypercholesterolemia (defined as any high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol ≥160 mg/dL, and triglyceride <150 mg/dL) groups. Blaha et al (2011) published another MESA report assessing 6760 patients with elevated high-sensitivity C-reactive protein as defined by the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin study; they found CIMT increases correlated with obesity but only mildly with high-sensitivity C-reactive protein.[21] Patel et al (2015) also reported on the MESA trial, which evaluated 6125 individuals with a family history of premature CHD, and identified 382 atherosclerotic CVD events at a mean follow-up of 10.2 years.[22] The study found that CAC data improved the risk estimation of atherosclerotic CVD events, but CIMT did not.

Camhi et al (2011) reported on the Bogalusa Heart Study (N=991) and found that obesity along with overweight and elevated metabolic risk were also associated with increased CIMT.[23] They also reported that in this study population, 41% of patients had increased CHD risk. In a study evaluating the association between clotting factor VII and CIMT (Coronary Artery Risk Development in Young Adults [CARDIA] study), clotting factor VII was associated with increases in CIMT in 1254 subjects.[24]

Barber et al (2015) reported on the BioImage study, which enrolled 5808 asymptomatic individuals from the U.S.[25] All patients were evaluated by 3-dimensional carotid ultrasound and by CAC score and followed for a mean of 2.7 years. The primary end point was major CV events, defined as CV death, MI, and ischemic stroke. Carotid plaque burden was an independent predictor of outcomes, with an HR of 2.36 (95% CI, 1.13-4.92) for individuals in the highest tertile. The CAC score was also an independent predictor of outcomes, with HRs similar to carotid plaque. Both carotid plaque and CAC score led to significant net reclassification, with a net reclassification index of 0.23.
Geisel et al (2017) conducted a prospective cohort study of 3108 patients without CVD upon entrance to the study.[26] All patients were evaluated for traditional risk factors of CVD; they were also assessed to calculate the CIMT, CAC score, and Ankle-Brachial Index score. During a mean follow-up of 10 years, 223 individuals suffered a major CV event (coronary event, stroke, CV death). All 3 methods helped predict adverse CV events. While CIMT was found to be higher in those who experienced an adverse CV event (0.76) than those who did not (0.69), CIMT did not significantly improve the prediction of cardiac risk for patients with an intermediate Framingham Risk Score.

Villines et al (2017) prospectively assessed a cohort of 3801 African American patients free of CVD at baseline.[27] Over a median follow-up of 9 years, there were 171 new cases of CVD and 339 deaths. The incidence of CV events correlated with changes in CIMT and participants in the highest CIMT quartile had the largest unadjusted incident rates of CVD for both men and women. However, risk reclassification improved only slightly when adding CIMT to a model that included only traditional risk factors for CVD.

Table 4. Summary of Key Prospective Cohort Clinical Validity Study Characteristics

Study	Study Population	Study Type	Country	Dates	Follow-Up
Chambless (1997)[15]	Asymptomatic for CHD	Prospective	US	1987-1993	Median 5.2 y
O'Leary (1999)[17]	Asymptomatic for CHD; ≥65 y	Prospective	US	1989-1993	Median 6.2 y
van der Meer (2004)[16]	Asymptomatic for CHD; ≥55 y	Cohort	EU	1990-1993	NR
Folsom (2008)[19]	Initially free of CVD	Cohort	US	2000-2007	Median 3.9 y
Baber (2015)[25]	Asymptomatic for CVD	Cohort	US, EU	2008-2009	Median 2.7 y
Lorenz (2010)[18]	Initially free of CVD	Retrospective	EU	NR	10 y
Geisel (2017)[26]	Initially free of CVD	Prospective	EU	2000-2003	Mean 10.3 ± 2.8 y
Villines (2017)[27]	African Americans without CVD	Prospective	US	2000-2011	Median 9 y

CHD: coronary heart disease; CVD: cardiovascular disease; EU: Europe; N: number; NR: not reported

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, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

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).

Johnson et al (2011) conducted a study by in which 55 patients, aged ≥ 40 years with 1 or more CAD risk factors, received carotid ultrasound screenings to determine prospectively whether abnormal results would change physician and patient behaviors.[28] Results were considered abnormal (when CIMT was >75th percentile or with the presence of carotid plaque) in 266 patients. Self-reported questionnaires were completed before the carotid ultrasound, immediately after the ultrasound, and 30 days later to assess behavioral changes. Physician behavior in prescribing aspirin ($p<.001$) and cholesterol medication ($p<.001$) changed significantly after identification of abnormal carotid ultrasound results. Abnormal ultrasound results predicted reduced dietary sodium (odds ratio [OR], 1.45; $p=.002$) and increased fiber intake (OR, 1.55, $p=.022$) in patients, but no other significant changes. Health outcomes were not evaluated in this study, and the short-term follow-up limits the interpretation of results.

Chain of Evidence

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.

The evidence on reclassification of CV risk offers a potential chain of evidence to improve outcomes. If a measure helps reclassify patients into risk categories that have different treatment approaches, then clinical management changes may occur that lead to improved outcomes. Because the ability to reclassify patients into clinically relevant categories with CIMT is modest at best, the clinical utility of this measure for reclassification is uncertain.

One study, however, aimed to estimate "normal" CIMT progression in order to identify subjects with faster atherosclerosis development. Olmastroni et al (2019) analyzed 1175 participants (36% men; mean age, 53 ± 11 years at baseline) with low to moderate CV risk.[29] The participants underwent 4 clinical evaluations and ultrasound CIMT determinations approximately every 4 years. Investigators assessed the growth of CIMT for each participant across the 12 years of the study using growth curve modeling. Results showed age to be the major factor in the significant slope observed for both mean CIMT and maximum CIMT models (mean: $\beta = 0.01$, $p<.001$; maximum: $\beta = 0.013$, $p<.001$). Sex also affected mean and maximum CIMT, with higher levels in men (mean: $\beta = -0.027$, $p<.001$; maximum: $\beta = -0.033$, $p<.001$). In addition, the age-dependent growth patterns differed between men and women. For women, menopausal status affected slopes. Women who were in menopause at the start of the study or who went through menopause during the follow-up had mean and maximum CIMT slopes that were similar to men's. Women with fertile status over the course of the study period progressed slowest. Other factors, such as smoking, systolic blood pressure, fasting glucose, and the presence of carotid atherosclerosis, predicted the speed of progression of both mean and maximum CIMT. The investigators noted that different mean and maximum CIMT curve slopes were seen in participants developing both carotid wall thickening and focal carotid atherosclerosis compared with the other participants. The results of this study demonstrated that estimated standard CIMT curves could be a useful tool for determining CV risk in asymptomatic low to intermediate-risk patients, allowing for earlier and more individualized preventive measures.

Section Summary: Ultrasonographic Measurement of Carotid Intima-Media Thickness
Evidence from large, prospective cohort studies and systematic reviews has established that CIMT is an independent risk factor for CAD. However, systematic reviews 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. There is no direct evidence on the clinical utility of measuring CIMT for cardiac risk stratification. The available evidence on reclassification into clinically relevant categories does not indicate that the use of CIMT will improve health outcomes. The objective of 1 study, however, was to define standard CIMT progression in low to moderate CV risk patients. Study results showed definite patterns related to various factors that could be used as a tool to earlier identify patients at increased CV risk.

SUMMARY OF EVIDENCE
For individuals who are undergoing cardiac risk assessment who receive ultrasonic measurement of CIMT, the evidence includes large cohort studies, case-control studies, and systematic reviews. Relevant outcomes are test accuracy and morbid events. Some studies have correlated increased CIMT with other commonly used markers for risk of CHD and with risk for future CV events. Lorenz et al (2012) found in their meta-analysis that CIMT was associated with increased CV events, although CIMT progression overtime was not associated

with increased CV event risk. Peters et al (2012) found that the added predictive value of CIMT was modest, and the ability to reclassify patients into clinically relevant categories was not demonstrated. The results from these reviews and other studies have demonstrated the predictive value of CIMT is uncertain and that the predictive ability for any level of population risk cannot be determined with precision. Also, available studies do not define how the 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 objective of 1 study, however, was to define “normal” CIMT progression in low to moderate CV risk patients. Study results showed definite patterns related to various factors that could be used as a tool to earlier identify patients at increased CV risk, but patient outcomes were not assessed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology and American Heart Association

In 2013, the guidelines from the American College of Cardiology and the American Heart Association on the assessment of cardiovascular (CV) risk did not recommend carotid intimal-medial thickness (CIMT) measurement in routine risk assessment of a first atherosclerotic cardiovascular disease event (class III: no benefit, level of evidence B).[30] This differs from their 2010 joint guidelines for the assessment of CV risk, which indicated CIMT might be reasonable for assessing CV risk in intermediate-risk asymptomatic adults.[31]

American Association of Clinical Endocrinologists

In 2017, the American Association of Clinical Endocrinologists and American College of Endocrinology published guidelines stating that CIMT could be applied as a risk stratification tool in determining the need for more aggressive preventive strategies against cardiovascular disease (grade B; best evidence level 2) but not routinely.[32]

American Society of Echocardiography

In 2008, the American Society of Echocardiography (ASE) consensus statement,[33] endorsed by the Society for Vascular Medicine, stated that CIMT is a feature of arterial wall aging “that is not synonymous with atherosclerosis, particularly in the absence of plaque.” The statement recommended measurement of both CIMT and carotid plaque by ultrasound “for refining CVD [cardiovascular disease] risk assessment in patients at intermediate cardiovascular disease risk (Framingham Risk Score 6%–20%) without established CHD [coronary heart disease], peripheral arterial disease, cerebrovascular disease, diabetes mellitus, or abdominal aortic aneurysm." However, the Society acknowledged that "More research is needed to determine whether improved risk prediction observed with CIMT or carotid plaque imaging translates into improved patient outcomes." The recommendations made in the 2008 consensus statement were endorsed in ASE's 2020 guideline entitled *Recommendations for the Assessment of Carotid Arterial Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk*.[34] Authors of the 2020 guideline also note the following: "Since the largest portion of CIMT (approximately 99% in healthy individuals and approximately 80% when diseased) consists of the medial layer, CIMT has not been shown to consistently add to CVD risk prediction."

U.S. Preventive Services Task Force Recommendations

In 2009, the USPSTF published a systematic review of CIMT within the scope of a larger recommendation on the use of nontraditional risk factors in coronary heart disease risk assessment.[35] The USPSTF could not draw conclusions on the applicability of CIMT to the intermediate-risk population at large outside the research setting. The USPSTF summary of recommendation specific to CIMT stated that: "… the current evidence is insufficient to assess the balance of benefits and harms of using … [CIMT] … to screen asymptomatic men and women with no history of CHD to prevent CHD events." The USPSTF identified the following research need: "The predictive value … of carotid IMT … should be examined in conjunction with traditional Framingham risk factors for predicting CHD events and death."

In 2018, the USPSTF published a recommendation statement on using nontraditional risk factors to assess the risk of cardiovascular disease; CIMT was not mentioned in this recommendation.[36]

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this policy are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01849575	Direct VIsualiZAtion of Asymptomatic Atherosclerotic Disease for Optimum Cardiovascular Prevention. A Population Based Pragmatic Randomised Controlled Trial Within Västerbotten Intervention Programme (VIP) and Ordinary Care (VIPVIZA)	3532	Dec 2027

NCT: national clinical trial.

Government Regulations
National:
There is no CMS national coverage determination (NCD) on this topic.

Local:
Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: Non-Invasive Cerebrovascular Studies (A57592)
Original Effective Date: 11/1/19
Revision Effective Date: 10/01/2021

The procedure code 93895 is listed as a Group 2, noncovered code.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Computed Tomography to Detect Coronary Artery Calcification
- Computerized 2-Lead Resting Electrocardiogram Analysis for the Diagnosis of Coronary Artery Disease
- Contrast-Enhanced Computed Tomography Angiography (CTA, CCTA, MDCT, MSCT) of the Heart and/or Coronary Arteries
- Genetic Testing - Gene Expression Testing in the Evaluation of Patients with Stable Ischemic Heart Disease
- Near-Infrared Spectroscopy-Intravascular Coronary Imaging
- Novel Biomarkers in the Risk Assessment and Management of Cardiovascular Disease

References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation. Feb 22 2022; 145(8): e153-e639. PMID 35078371 https://www.ahajournals.org/doi/10.1161/CIR.0000000000001052 Accessed June 15, 2022.
2. Pasternak RC. Report of the Adult Treatment Panel III: the 2001 National Cholesterol Education Program guidelines on the detection, evaluation and treatment of elevated cholesterol in adults. Cardiol Clin. Aug 2003; 21(3): 393-8. PMID 14621453
3. Mookadam F, Moustafa SE, Lester SJ, et al. Subclinical atherosclerosis: evolving role of carotid intima-media thickness. Prev Cardiol. 2010; 13(4): 186-97. PMID 20860643
4. Den Ruijter HM, Peters SA, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. Aug 22 2012; 308(8): 796-803. PMID 22910757

5. Lorenz MW, Polak JF, Kavousi M, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet. Jun 2 2012;379(9831): 2053-2062. PMID 22541275
6. van den Oord SC, Sijbrands EJ, ten Kate GL, et al. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. Atherosclerosis. May 2013;228(1):1-11. PMID 23395523
7. Bytyci I, Shenouda R, Wester P, et al. Carotid Atherosclerosis in Predicting Coronary Artery Disease: A Systematic Review and Meta-Analysis. Arterioscler Thromb Vasc Biol. Apr 2021; 41(4): e224-e237. PMID 33626907
8. Tschiderer L, Klingenschmid G, Seekircher L, et al. Carotid intima-media thickness predicts carotid plaque development: Meta-analysis of seven studies involving 9341 participants. Eur J Clin Invest. Apr 2020; 50(4): e13217. PMID 32112400
9. Plichart M, Celermajer DS, Zureik M, et al. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. Atherosclerosis. Dec 2011; 219(2):917-24. PMID 22005196
10. Keo HH, Baumgartner I, Hirsch AT, et al. Carotid plaque and intima-media thickness and the incidence of ischemic events in patients with atherosclerotic vascular disease. Vasc Med Oct 2011; 16(5):323- 30. PMID 21908682
11. Nambi V, Chambless L, He M, et al. Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. Eur Heart J. Jan 2012; 33(2):183-90. PMID 21666250
12. Xie W, Liang L, Zhao L, et al. Combination of carotid intima-media thickness and plaque for better predicting risk of ischaemic cardiovascular events. Heart. Aug 2011; 97(16):1326-31. PMID 21653216
13. Peters SA, den Ruijter HM, Bots ML, et al. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart. Feb 2012;98(3):177-184. PMID 22095617
14. Dobs AS, Nieto FJ, Szklo M, et al. Risk factors for popliteal and carotid wall thicknesses in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. Nov 15 1999; 150(10):1055-67. PMID 10568620
15. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol. Sep 15 1997; 146(6):483-94. PMID 9290509
16. van der Meer IM, Bots ML, Hofman A, et al. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. Circulation. Mar 09 2004; 109(9):1089-94. PMID 14993130
17. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. Jan 07 1999; 340(1):14-22. PMID 9878640
18. Lorenz MW, Schaefer C, Steinmetz H, et al. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). Eur Heart J. Aug 2010; 31(16):2041-8. PMID 20530503
19. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the

Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. Jun 23 2008; 168(12):1333-9. PMID 18574091
20. Paramsothy P, Knopp RH, Bertoni AG, et al. Association of combinations of lipid parameters with carotid intima-media thickness and coronary artery calcium in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. Sep 21 2010; 56(13):1034-41. PMID 20846602
21. Blaha MJ, Rivera JJ, Budoff MJ, et al. Association between obesity, high-sensitivity C-reactive protein ≥2 mg/L, and subclinical atherosclerosis: implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. Jun 2011; 31(6):1430-8. PMID 21474823
22. Patel J, Al Rifai M, Blaha MJ, et al. Coronary artery calcium improves risk assessment in adults with a family history of premature coronary heart disease: results from Multiethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. Jun 2015;8(6):e003186. PMID 26047825
23. Camhi SM, Katzmarzyk PT, Broyles ST, et al. Subclinical atherosclerosis and metabolic risk: role of body mass index and waist circumference. Metab Syndr Relat Disord. Apr 2011; 9(2):119-25. PMID 21133775
24. Green D, Foiles N, Chan C, et al. An association between clotting factor VII and carotid intima-media thickness: the CARDIA study. Stroke. Jul 2010; 41(7):1417-22. PMID 20466994
25. Baber U, Mehran R, Sartori S, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol. Mar 24 2015;65(11):1065-1074. PMID 25790876
26. .Geisel MH, Bauer M, Hennig F, et al. Comparison of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for predicting 10-year incident cardiovascular events in the general population. Eur Heart J. Jun 14 2017;38(23):1815-1822. PMID 28379333
27. Villines TC, Hsu LL, Blackshear C, et al. Relation of carotid intima-media thickness to cardiovascular events in Black Americans (From the Jackson Heart Study). Am J Cardiol. Nov 1 2017;120(9):1528-1532. PMID 28844515
28. Johnson HM, Turke TL, Grossklaus M, et al. Effects of an office-based carotid ultrasound screening intervention. J Am Soc Echocardiogr. Jul 2011;24(7):738-747. PMID 21477989
29. Olmastroni E, Baragetti A, Casula M, et al. Multilevel models to estimate carotid intima-media thickness curves for individual cardiovascular risk evaluation. Stroke. Jul 2019; 50(7): 1758-1765. PMID 31164073
30. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. Jun 24 2014; 129(25 Suppl 2): S49-73. PMID 24222018
31. Greenland P, Alpert JS, Beller GA et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Dec 14 2010; 56(25):e50-103. PMID 21144964
32. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease - Executive Summary Complete appendix to Guidelines available at journals.aace.com Endocr Pract. Apr 2 2017;23(4):479-497. PMID 28156151

33. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. Feb 2008;21(2):93-111; quiz 189-190. PMID 18261694
34. Johri AM, Nambi V, Naqvi TZ, et al. Recommendations for the Assessment of Carotid Arterial Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk: From the American Society of Echocardiography. J Am Soc Echocardiogr. Aug 2020; 33(8): 917-933. PMID 32600741
35. Calonge N, Petitti DB, DeWitt TG, et al. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. Oct 06 2009; 151(7):474-82. PMID 19805770
36. Curry SJ, Krist AH, Owens DK, et al. Risk assessment for cardiovascular disease with nontraditional risk factors: US Preventive Services Task Force Recommendation Statement. JAMA. Jul 17 2018; 320(3): 272-280. PMID 29998297

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 6/15/22, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/07	3/21/07	5/1/07	Joint policy established
5/1/08	2/19/08	5/1/08	Routine maintenance
5/1/09	2/10/09	2/10/09	Routine maintenance
3/1/12	12/13/11	12/21/11	Routine maintenance
9/1/13	6/19/13	6/26/13	Routine maintenance Policy title changed from “Carotid Artery Intima-Media Thickness Study” to “Ultrasonographic Measurement of Carotid Intima-Medial Thickness as an Assessment of Subclinical Atherosclerosis.”
1/1/15	10/24/14	11/3/14	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance Added procedure code 93895
5/1/17	2/21/17	2/21/17	Routine maintenance
5/1/18	2/20/18	2/20/18	Routine maintenance
5/1/19	2/19/19		Routine maintenance
5/1/20	2/18/20		Routine maintenance
5/1/21	2/16/21		Routine maintenance Ref 2,3,4,28,29,34 added (28 and 34 are new, others were used in previous reviews) Code 0126T deleted; 93998 added
11/1/21	8/17/21		Routine maintenance Ref 1,7,8,35 added
11/1/22	8/16/22		Routine maintenance Ref 1 added (ls)

Next Review Date: 3rd Qtr, 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ULTRASONOGRAPHIC MEASUREMENT OF CAROTID INTIMA-MEDIAL THICKNESS AS AN ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member’s certificate and is not guaranteed. Please consult the individual member’s certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.