Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

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

Professional
Original Effective Date: February 27, 2007
Revision Date(s): August 24, 2009; September 6, 2011, September 18, 2012; January 1, 2015; October 13, 2015; February 15, 2017; August 1, 2018
Current Effective Date: February 27, 2007

Institutional
Original Effective Date: September 23, 2009
Revision Date(s): September 6, 2011; September 18, 2012; January 1, 2015; October 13, 2015; February 15, 2017; August 1, 2018
Current Effective Date: September 23, 2009

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are undergoing cardiac risk assessment	Interventions of interest are: • Ultrasonic measurement of carotid intima-medial thickness	Comparators of interest are: • Standard of care • Alternative cardiovascular risk predictors	Relevant outcomes include: • Test accuracy • Morbid events

DESCRIPTION

Ultrasonographic measurement of carotid intima-medial (or intimal-media) thickness (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.

Objective

The objective of this evidence review is to evaluate whether results of ultrasonographic measurement of carotid intima-medial thickness improve risk categorization in individuals who are undergoing cardiac risk assessment.

Background

Coronary Heart Disease

Coronary heart disease (CHD) accounts for 30.8% of all deaths in the United States.[1] 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.

Diagnosis

The third report of the NCEP Adult Treatment Panel (ATP III) established various treatment strategies to modify the risk of CHD, with emphasis on target goals of LDL-C. Pathology studies have demonstrated that levels of traditional risk factors are associated with the extent and severity of atherosclerosis. ATP III 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 interest in identifying a technique that can improve the ability to diagnose those at risk of developing CHD, as well as 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-medial thickness (CIMT) has been investigated as a technique to identify and monitor subclinical atherosclerosis. B-mode ultrasound is most commonly used to measure CIMT. The intima-medial 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 2 lines constitutes the IMT.

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 IMT 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.

POLICY

Ultrasonographic measurement of carotid artery intima-medial thickness as a technique for identifying subclinical atherosclerosis is considered **experimental / investigational** for use in the screening, diagnosis, or management of atherosclerotic disease.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through April 5, 2018.

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.

The literature on the use of carotid intima-media thickness (CIMT) for cardiac risk stratification consists of numerous cohort studies and systematic reviews of these cohort studies. The following review includes the largest prospective cohort studies and the most important systematic reviews of these studies.

Ultrasonographic Mmeasurement of CIMT

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does CIMT improve risk categorization in individuals who are undergoing a cardiac risk assessment?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The test being considered is an ultrasonographic measurement of CIMT.

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 10-year studies are of particular interest due to the prolonged natural history of cardiovascular disease.

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

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Systematic Reviews
Mookadam et al (2010) conducted a systematic review of the role of CIMT in predicting individual cardiovascular event risk, and as a tool for assessing therapeutic interventions.[3] Reviewers concluded that CIMT is an independent risk factor for cardiovascular events and may be useful in determining treatment when there is uncertainty regarding the approach or patient reluctance. However, they recommended further study to identify the best approaches to screening and interventions to prevent progression of atherosclerosis.

In 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] Using individual data for 45,828 patients from 14 population-based cohort studies, Den Ruijter et al (2012) found 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

to 0.766) and women (0.757; 95% CI, 0.749 to 0.764), suggesting the addition of CIMT in risk assessment offered limited benefit.

In another meta-analysis of individual participant data pooled from 16 studies (total N=36,984 patients), Lorenz et al (2012) 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 MI, and 2028 combined end points (MI, stroke, vascular death) occurred. Mean CIMT of the 2 ultrasound results was predictive of cardiovascular 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 cardiovascular 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 cardiovascular risk but did not demonstrate that changes in CIMT over time are predictive of future events.

A meta-analysis of 15 articles by van den Oord et al (2013) found similar results on the added value of CIMT.[6] Six cohort studies (total N=32,299 patients) were evaluated to examine the predictive value of CIMT when added to traditional cardiovascular risk factors. While 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 improve risk prediction over traditional cardiovascular risk factors (p=0.8).

Studies have found that including carotid plaques in CIMT measurements improved the predictive value of cardiovascular risk over CIMT assessed only in plaque-free sites.[7-10] However, the meta-analysis by Lorenz found no difference in the main results between studies that included CIMT with carotid plaque and plaque-free CIMT.[5] The systematic review by Peters et al (2012) found adding carotid plaque to the traditional CIMT model increased the C statistic from 0.01 to 0.06.[11]

Prospective Cohort Studies

Numerous prospective cohort studies have evaluated the association between CIMT and future cardiovascular 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.[12] CIMT had a graded relation with increasing quartiles of plasma total cholesterol, low-density lipoprotein cholesterol, and triglycerides. CIMT also correlated with the incidence of coronary heart disease (CHD) in a subgroup of patients enrolled in the trial after 4 to 7 years of follow-up.[13] 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. 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 ages 55 years and older. 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 progression of atherosclerosis in asymptomatic elderly subjects is a

prelude to cardiovascular events. Measurements of CIMT were used to assess the progression of atherosclerosis. Increasing CIMT was associated with increased risks of stroke and MI.[14]

OLeary et al (1999) performed CIMT measurement on 4476 asymptomatic subjects ages 65 years or older without clinical CVD in the Cardiovascular Health Study.[15] The incidence of cardiovascular events correlated with measurements of CIMT; this association remained significant after adjusting for traditional risk factors. Authors concluded that increases in CIMT were 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, 7.1-10.0 years). Adverse events were MI in 73 (1.5%) patients, angina or MI in 271 (5.5%) patients, and death in 72 (1.5%) subjects. Lorenz et al (2010) retrospectively reviewed Carotid Atherosclerosis Progression Study data.[16] They modeled the predictive value of CIMT on the cardiovascular 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. Trialists 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 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.[17] In a report from the MESA trial by Paramsothy et al (2010), CIMT results in 4792 healthy, nondiabetic adults who were not on lipid-lowering medications were compared across 6 different lipid groups, including normolipemia and several types of common dyslipidemias.[18] 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. In another MESA report, assessing 6760 patients with elevated high-sensitivity C-reactive protein as defined by the JUPITER study, Blaha et al (2011) found CIMT increases correlated with obesity but only mildly with high-sensitivity C-reactive protein.[19] A report from MESA trial by Patel et al (2015), which evaluated 6125 individuals with a family history of premature CHD, identified 382 atherosclerotic CVD events at a mean follow-up of 10.2 years.[20] The study found that CAC data improved the risk estimation of atherosclerotic CVD events, but CIMT did not.

In the Bogalusa Heart Study (N=991 subjects), obesity along with overweight and elevated metabolic risk were associated with increased CIMT.[21] In this study population, Camhi et al (2011) found that 41% of patients had increased CHD risk. In the CARDIA study, clotting factor VII was associated with increases in CIMT in 1254 subjects.[22] CIMT has also been used as a surrogate outcome measure in atherosclerosis treatment research studies.[23]

Raiko et al (2010) compared CAD risk scoring tools for identification of CHD risk with CIMT results in 2204 healthy adults, ages 24 to 39 years, from the Cardiovascular Risk in Young Finns study.[24] 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.

The BioImage study, reported by Baber et al (2015), enrolled 5808 asymptomatic individuals from the United States.[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 cardiovascular events, defined as cardiovascular death, MI, and ischemic stroke. Carotid plaque burden was an independent predictor of outcomes, with an HR of 2.36 (95% CI, 1.13 to 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 on 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 cardiovascular event (coronary event, stroke, CV death). All 3 methods helped predict adverse cardiovascular events. While CIMT was found to be higher in those who experienced an adverse cardiovascular 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 cardiovascular 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.

Section Summary: Clinically Valid

Evidence from large, prospective cohort studies has established that CIMT is an independent risk factor for CAD. However, systematic reviews have shown that 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.

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

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.

In a study by Johnson et al (2011), 355 patients, ages 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 ($p<0.001$) and cholesterol medication ($p<0.001$) changed significantly after identification of abnormal carotid ultrasound results. Abnormal ultrasound results predicted reduced dietary sodium (odds ratio, 1.45; $p=0.002$) and increased fiber intake (odds ratio, 1.55, $p=0.022$) in patients, but no other significant changes. Health outcomes were not evaluated in this study, and the short-term follow-up limits 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 the reclassification of cardiovascular 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.

Section Summary: Clinically Useful

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 use of CIMT will improve health outcomes.

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 cardiovascular events. A meta-analysis of individual patient data by Lorenz et al (2012) found that CIMT was associated with increased cardiovascular events although CIMT progression over time was not associated with increased cardiovascular event risk. In a systematic review by Peters et al (2012), 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 evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American College of Cardiology and American Heart Association

The 2013 guidelines on the assessment of cardiovascular risk from the American College of Cardiology and the American Heart Association 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).[29] This differs from their 2010 joint guidelines for assessment of cardiovascular risk, which indicated CIMT might be reasonable for assessing cardiovascular risk in intermediate-risk asymptomatic adults.[30]

American Association of Clinical Endocrinologists et al

The American Association of Clinical Endocrinologists and American College of Endocrinology published guidelines (2017) 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.[31]

American Society of Echocardiography

The American Society of Echocardiography (2008) consensus statement,[32] 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, 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."

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2009; 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.[33] 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." 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."

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. 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	3200	Jun 2021

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

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

0126T Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment

- There is a CPT category I code specific to the combination of CIMT and carotid atheroma evaluation: 93895.
- There is also a CPT category III code specific to this test: 0126T.

DIAGNOSIS

Experimental / investigational for all diagnoses related to this policy.

REVISIONS	
08-24-2009	Policy added to the bcbsks.com web site.
09-06-2011	Description section updated
	Rationale section updated
	In Coding section ▪ Added the instructional phrase "It is possible that providers might incorrectly use CPT code 93880, which describes bilateral duplex scan of extracranial arteries."
	References updated
09-18-2012	Description section updated
	Rationale section updated
	References updated
01-01-2015	Policy posted 01-16-2015
	In Coding section:

REVISIONS	
	▪ Added CPT Code: 93895 (Effective January 1, 2015)
10-13-2015	Description section updated
	Rationale section updated
	References updated
02-15-2017	Description section updated
	In Policy section: ▪ Removed "CIMT" abbreviation.
	Rationale section updated
	In Coding section: ▪ Coding notations updated
	References updated
08-01-2018	Description section updated
	Rationale section updated
	References updated

REFERENCES

1. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. Jan 26 2016;133(4):e38-360. PMID 26673558
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):393-398. PMID 14621453
3. Mookadam F, Moustafa SE, Lester SJ, et al. Subclinical atherosclerosis: evolving role of carotid intima-media thickness. Prev Cardiol. Fall 2010;13(4):186-197. 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. 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):917-924. PMID 22005196
8. 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):323-330. PMID 21908682
9. 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):183-190. PMID 21666250
10. 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):1326-1331. PMID 21653216
11. 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

12. 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):1055-1067. PMID 10568620
13. 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):483-494. PMID 9290509
14. 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 9 2004;109(9):1089-1094. PMID 14993130
15. 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 7 1999;340(1):14-22. PMID 9878640
16. 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):2041-2048. PMID 20530503
17. 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):1333-1339. PMID 18574091
18. 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):1034-1041. PMID 20846602
19. 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):1430-1438. PMID 21474823
20. 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
21. 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):119-125. PMID 21133775
22. 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):1417-1422. PMID 20466994
23. Bots ML, Palmer MK, Dogan S, et al. Intensive lipid lowering may reduce progression of carotid atherosclerosis within 12 months of treatment: the METEOR study. J Intern Med. Jun 2009;265(6):698-707. PMID 19298496
24. Raiko JR, Magnussen CG, Kivimaki M, et al. Cardiovascular risk scores in the prediction of subclinical atherosclerosis in young adults: evidence from the cardiovascular risk in a young Finns study. Eur J Cardiovasc Prev Rehabil. Oct 2010;17(5):549-555. PMID 20354441
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. Goff DC, Jr., 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. Nov 12 2013. PMID 24222018

30. 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
31. 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 - Executive Summary. Endocr Pract. Apr 2 2017;23(4):479-497. PMID 28156151
32. 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
33. U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. Oct 6 2009;151(7):474-482. PMID 19805770