Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual

Topic: Ultrasonographic Measurement of Carotid Artery Intima-Media Thickness as an Assessment of Atherosclerosis

Date of Origin: April 2, 2002

Section: Radiology

Last Reviewed Date: December 2013

Policy No: 37

Effective Date: March 1, 2014

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Coronary heart disease accounts for 27% of all deaths in the United States.[1] Established major risk factors for coronary heart disease (CHD) have been identified by the National Cholesterol Education Program (NCEP) Expert Panel and include elevated serum levels of low-density lipoprotein (LDL) cholesterol and total cholesterol, and low serum levels of high-density lipoprotein (HDL) cholesterol. Other risk factors include a history of cigarette smoking, hypertension, family history of premature CHD, and age. Pathology studies have demonstrated that levels of traditional risk factors are associated with the extent and severity of atherosclerosis. 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. Therefore, 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.

Ultrasonographic measurement of carotid intima-medial (also called intimal-medial or intima-media) thickness (CIMT) refers to the use of B-mode ultrasound to determine the thickness of the two innermost layers of the carotid artery wall, the intima and the media. Ultrasonographic measurement of CIMT has been investigated as a proxy for progression of atherosclerosis and is proposed for use in identifying and monitoring subclinical CHD.

Regulatory Status

In February 2003, SonoCalc® (SonoMetric Health, LLC) was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this software was substantially equivalent to image display products from existing ultrasound systems. Subsequently, several other devices have been approved through the 510(k) process.

Note: this policy does not address carotid artery ultrasound for the evaluation of a cerebrovascular condition suspected on the basis of abnormal signs or symptoms, which is considered a standard of care.

MEDICAL POLICY CRITERIA

Ultrasonographic measurement of the carotid artery intima-media thickness is considered **investigational** for screening, diagnosis, and management of atherosclerotic disease.

SCIENTIFIC EVIDENCE

Currently, screening and monitoring for coronary artery disease in clinically asymptomatic individuals is achieved through administration of standard risk assessment measures (including family history and non-invasive testing). Within this context, assessment of the proposed use of ultrasonographic measurement of carotid intima-media thickness (CIMT) must fulfill three parameters:

1) Establish technical feasibility, typically assessed with two types of studies, those that compare test measurements with a gold standard and those that compare results taken with the same device on different occasions (test-retest). Normally conducted in the pre-clinical setting, the focus of this parameter is on test reproducibility and establishment of the test protocol.

2) Demonstrate diagnostic performance (sensitivity, specificity, positive and negative predictive values) of the test compared with the gold standard.

3) Evaluate clinical outcomes based on the performance of the test versus the standard of care. While in some cases, new diagnostic tests can be adequately evaluated using technical and diagnostic performance, when a test identifies a new or different group of patients with a disease, randomized trials are needed to demonstrate the impact of the test on net health outcomes.

Literature Appraisal

<u>Diagnostic Utility (Analytical and Clinical Validity)</u>

The current literature consists of several systematic reviews, meta-analyses, and case series related to technical feasibility, and large longitudinal cohort studies conducted in the research setting.

Systematic Reviews and Meta-analyses

Three systematic reviews[2-4] and 3 meta-analyses[5-7] analyzed the ability of CIMT measurement to identify coronary artery disease in asymptomatic patients and predict first-time myocardial infarction (MI) or first-time stroke. The inclusion criteria for the studies included in these reviews varied. However, the results consistently reported that, while CIMT is a predictor of cardiovascular risk, the addition of CIMT measurement did not significantly improve risk prediction over conventional cardiovascular risk factors. In addition, most of the reviewed studies were conducted in the research setting and therefore cannot be used to draw conclusions on the applicability of CIMT measurement in the clinical setting for asymptomatic patients at large.

Randomized Controlled Trials (RCTs)

There are no RCTs evaluating the analytical or clinical validity of ultrasonographic measurement of CIMT.

Nonrandomized Studies

- Technical feasibility was addressed in a 2010 study on inter-reader differences in measuring CIMT.[8] Among 5 readers with 6 months to 6 years of experience reading CIMT images, significant differences were seen in the measurement of 26 CIMT images, whose final measurements ranged from 0.57–0.78 mm. This range corresponds to as much as a 21 year vascular age discrepancy in the same image, a high degree of error. The authors suggest improved training of CIMT readers, or the development of an IMT edge-reader before this technology is adopted in the clinical setting.
- An observational study among 320 Spanish patients compared CIMT measurements with traditional risk assessment measures (age, hypertension and systolic blood pressure).[9] Although CHD risk was reclassified for 18% of participants based on CIMT, implications for clinical management and effect on health outcomes were not reported.

- A small case-control study among young asymptomatic hypertensive and non-hypertensive Egyptians reported a relationship between CIMT and hypertension and family history of hypertension.[10] The study design was cross-sectional (no follow-up), and clinically relevant outcomes were not reported, making the implication of these findings unclear.

- In the Atherosclerosis Risk in Communities (ARIC) study, a large observation study conducted in the research setting, the authors evaluated risk factors associated with increased carotid IMT in 15,800 subjects.[11] CIMT had a graded relationship with increasing quartiles of plasma total cholesterol, LDL cholesterol, and triglycerides. CIMT was 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.[12] The researchers defined and compared extreme carotid IMT (i.e., >/= 0.1mm) to non-extreme IMT (i.e., < 0.1mm) and found a relationship between CIMT and CHD events. Nevertheless, this definition of extreme IMT has yet to be tested in the clinical setting.

- Several other studies have used carotid IMT measurements as outcome measures.[13-23] Due to limitations such as the lack of a shared diagnostic CIMT measurement protocol, lack of head-to-head comparisons with gold standard diagnostic tests for CHD, and unknown impact of CIMT measurement on clinical decision-making and primary health outcomes, these studies do not add to the understanding of the net effect of this testing on the diagnosis and treatment of CHD.

- More recent studies reported that including carotid plaques in CIMT increased the predictive value of cardiovascular risk over CIMT assessed only in plaque-free sites.[24-27] 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 found adding carotid plaque to the traditional CIMT model increased the c-statistic from 0.01 to 0.06.[2]

Clinical Utility

Randomized Controlled Trials (RCTs)

There are no RCTs investigating the clinical utility of measuring CIMT for cardiac risk stratification.

Nonrandomized Study

In a 2011 study by Johnson and colleagues, 355 patients, aged 40 years with 1 or more cardiovascular disease risk factor, received carotid ultrasound screenings to prospectively determine whether abnormal results would change physician and patient behaviors.[28] Results were considered abnormal in 266 patients (CIMT greater than the 75th percentile or the presence of carotid plaque). Self- reported questionnaires were completed before the carotid ultrasound, immediately after the ultrasound and 30 days later to determine behavioral changes. Physician behavior in prescribing aspirin and cholesterol medication changed significantly ($p < 0.001$ and $p < 0.001$, respectively) 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 interpretation of results.

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

Clinical Practice Guidelines

American College of Cardiology Foundation and the American Heart Association Task Force (ACGF/AHA)

In 2010, the ACGF/AHA Task Force on Practice Guidelines issued a joint clinical practice guideline for the assessment of cardiovascular risk in asymptomatic adults.[29] The guideline gave CIMT a class IIa recommendation, stating, “Measurement of carotid artery IMT is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk.” A class IIa recommendation is one in “favor of treatment or procedure being useful/effective.” The guideline cites B-level evidence for this recommendation, defined as “limited populations evaluated” or “some conflicting evidence from single randomized trial or nonrandomized studies.” Conclusions at the end of this recommendation cite the lack of evidence regarding clinical utility of CIMT, along with uncertainty in this test’s location in the diagnostic hierarchy of atherosclerosis.

U.S. Preventive Services Task Force (USPSTF)[30]

Based on the systematic review[4] conducted for the USPSTF, the Task Force “concludes 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 identifies 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."

American Society of Echocardiography (ASE)[31]

The ASE consensus statement endorsed by the Society for Vascular Medicine, states that CIMT is a feature of arterial wall aging "that is not synonymous with atherosclerosis, particularly in the absence of plaque." The statement, and a comment on the statement published in 2009, recommend measurement of both CIMT and carotid plaque by ultrasound among patients at risk of CHD, or with a family history of CHD, where results will be expected to alter therapy.[32] In their conclusion, the authors acknowledge that, "More research is needed to determine whether improved risk prediction observed with CIMT or carotid plaque imaging translates into improved patient outcomes." In the disclosure section of both papers, the primary and secondary authors (same for both publications) disclose ties to Siemens Medical Solutions, a manufacturer of a CIMT measurement device (the syngo® Arterial Health Package). In addition, the primary author has disclosed intellectual property rights relating to carotid ultrasound and CHD risk assessment.

- The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) does not recommend using "emerging risk factors" in assessment of persons for primary prevention. It does state that "emerging risk factors" may be useful in certain patient-centered circumstances.[33]

Summary

Although studies have mainly been in agreement that carotid artery intima-medial thickness (CIMT) is associated with risk of coronary heart disease (CHD), the degree to which this information informs clinical decision making has not been established. At the present time there are no scientific studies that directly and experimentally test the hypothesis that measurement of CIMT results in improved patient outcomes. Protocols relating to risk adjustment based on CIMT thickness have not been established, and there is no specific guidance on how measurements of CIMT should be incorporated into risk assessment and risk management. Prospective randomized controlled trials on this technology are needed to answer these questions. Because the existing data are insufficient to determine the impact of this technology on net health outcomes (CHD events and long-term survival), measurement of CIMT for screening, diagnosis, and management of cardiovascular disease is considered investigational.

REFERENCES

1. Minino, AM, Heron, MP, Murphy, SL, Kochanek, KD. Deaths: final data for 2004. *Natl Vital Stat Rep*. 2007 Aug 21;55(19):1-119. PMID: 17867520
2. Peters, SA, den Ruijter, HM, Bots, ML, Moons, KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart*. 2012 Feb;98(3):177-84. PMID: 22095617
3. Mookadam, F, Moustafa, SE, Lester, SJ, Warsame, T. Subclinical atherosclerosis: evolving role of carotid intima-media thickness. *Prev Cardiol*. 2010 Fall;13(4):186-97. PMID: 20860643
4. Helfand, M, Buckley, DI, Freeman, M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009 Oct 6;151(7):496-507. PMID: 19805772

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*. 2012 Jun 2;379(9831):2053-62. PMID: 22541275
6. Den Ruijter, HM, Peters, SA, Anderson, TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012;308:796-803. PMID: 22910757
7. 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*. 2013 May;228(1):1-11. PMID: 23395523
8. Polak, JF, Funk, LC, O'Leary, DH. Inter-reader differences in common carotid artery intima-media thickness: implications for cardiovascular risk assessment and vascular age determination. *J Ultrasound Med*. 2011 Jul;30(7):915-20. PMID: 21705724
9. Aguilar-Shea, AL, Gallardo-Mayo, C, Garrido-Elustondo, S, Calvo-Manuel, E, Zamorano-Gomez, JL. Carotid intima-media thickness as a screening tool in cardiovascular primary prevention. *Eur J Clin Invest*. 2011 May;41(5):521-6. PMID: 21155766
10. Mahfouz, RA, El Tahlawi, MA, Ateya, AA, Elsaied, A. Early detection of silent ischemia and diastolic dysfunction in asymptomatic young hypertensive patients. *Echocardiography*. 2011 May;28(5):564-9. PMID: 21426396
11. Dobs, AS, Nieto, FJ, Szklo, M, Barnes, R, Sharrett, AR, Ko, WJ. Risk factors for popliteal and carotid wall thicknesses in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol*. 1999 Nov 15;150(10):1055-67. PMID: 10568620
12. 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*. 1997 Sep 15;146(6):483-94. PMID: 9290509
13. van der Meer, IM, Bots, ML, Hofman, A, del Sol, AI, van der Kuip, DA, Witteman, JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. *Circulation*. 2004 Mar 9;109(9):1089-94. PMID: 14993130
14. 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*. 2010 Sep 21;56(13):1034-41. PMID: 20846602
15. 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*. 2011 Jun;31(6):1430-8. PMID: 21474823
16. Blankstein, R, Budoff, MJ, Shaw, LJ, et al. Predictors of coronary heart disease events among asymptomatic persons with low low-density lipoprotein cholesterol MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2011 Jul 19;58(4):364-74. PMID: 21757113
17. 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*. 2011 Apr;9(2):119-25. PMID: 21133775
18. Green, D, Foiles, N, Chan, C, Kang, J, Schreiner, PJ, Liu, K. An association between clotting factor VII and carotid intima-media thickness: the CARDIA study. *Stroke*. 2010 Jul;41(7):1417-22. PMID: 20466994
19. Probstfield, JL, Margitic, SE, Byington, RP, Espeland, MA, Furberg, CD. Results of the primary outcome measure and clinical events from the Asymptomatic Carotid Artery Progression Study. *Am J Cardiol*. 1995 Sep 28;76(9):47C-53C. PMID: 7572686

20. Byington, RP, Evans, GW, Espeland, MA, et al. Effects of lovastatin and warfarin on early carotid atherosclerosis: sex-specific analyses. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation*. 1999 Jul 20;100(3):e14-7. PMID: 10411862
21. Hodis, HN, Mack, WJ, LaBree, L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med*. 1996 Mar 15;124(6):548-56. PMID: 8597317
22. 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*. 2010 Oct;17(5):549-55. PMID: 20354441
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*. 2009 Jun;265(6):698-707. PMID: 19298496
24. 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*. 2011 Dec;219(2):917-24. PMID: 22005196
25. 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*. 2011 Oct;16(5):323-30. PMID: 21908682
26. 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*. 2012 Jan;33(2):183-90. PMID: 21666250
27. 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*. 2011 Aug;97(16):1326-31. PMID: 21653216
28. Johnson, HM, Turke, TL, Grossklaus, M, et al. Effects of an office-based carotid ultrasound screening intervention. *J Am Soc Echocardiogr*. 2011 Jul;24(7):738-47. PMID: 21477989
29. 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*. 2010 Dec 14;56(25):e50-103. PMID: 21144964
30. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009 Oct 6;151(7):474-82. PMID: 19805770
31. 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*. 2008 Feb;21(2):93-111; quiz 89-90. PMID: 18261694
32. Stein, JH, Korcarz, CE, Post, WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: summary and discussion of the American Society of Echocardiography consensus statement. *Prev Cardiol*. 2009 Winter;12(1):34-8. PMID: 19301689
33. 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*. 2003 Aug;21(3):393-8. PMID: 14621453
34. BlueCross BlueShield Association Medical Policy Reference Manual "Ultrasonographic Measurement of Carotid Intimal-Medial Thickness as an Assessment of Subclinical Atherosclerosis." Policy No. 2.02.16

CROSS REFERENCES

Computed Tomography to Detect Coronary Artery Calcifications, Radiology, Policy No. 6

Contrast-Enhanced Computed Tomographic Angiography (CTA) for Coronary Artery Evaluation, Radiology, Policy No. 46

CODES	NUMBER	DESCRIPTION
Note: CPT 93880 (duplex scan of extracranial arteries; complete bilateral study) should not be used to identify carotid intima-media thickness studies.		
CPT	0126T	Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment