BlueCross BlueShield of Vermont
An Independent Licensee of the Blue Cross and Blue Shield Association.

Corporate Medical Policy

Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease

File name: Homocysteine Testing in the screening, diagnosis and management of cardiovascular disease
File code: UM.DIAG.02
Origination: 1/2011
Last Review: 03/2014 (icd-10 remediation only)
Effective Date: 07/01/2011

Document Precedence

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract language, the member's contract language takes precedence.

Medical Policy

Description

Homocysteine is a sulfur-containing amino acid that is rapidly oxidized in plasma into homocysteine and cysteine-homocysteine disulfide. Measurement of total plasma homocysteine is the sum of homocysteine and its oxidized forms. The laboratory test is referred to as either homocysteine or homocyst(e)ine.

Plasma levels of homocysteine have been actively researched as a risk factor for cardiovascular disease, initially based on the observation that patients with hereditary homocystinuria, an inborn error of metabolism associated with high plasma levels of homocysteine, had a markedly increased risk of cardiovascular disease. Subsequently, prospective epidemiologic studies were conducted to determine if an elevated plasma level of homocysteine was an independent risk factor for cardiovascular disease, and could be used to improve current risk prediction models.

Interest in homocysteine as a potentially modifiable risk factor has been stimulated by the epidemiologic finding that levels of homocysteine are inversely correlated with levels of folate. This finding has raised the possibility that treatment with folic acid might lower homocysteine levels and, in turn, reduce the risk of coronary artery disease (CAD). Therefore, homocysteine has potential utility both as a risk predictor and as a target of treatment.

Policy

Measurement of plasma levels of homocysteine is considered **investigational** in the screening, evaluation, and management of patients for cardiovascular disease.

Homocysteine testing may be medically necessary for the following indications:

- Evaluating persons with homocystinuria (cystathionine beta synthetase deficiency)
- Evaluating persons with coagulation disorders (e.g. unexplained thrombotic disorders such as deep venous thrombosis or pulmonary embolism
- Evaluating women with recurrent pregnancy loss
- Evaluating persons with borderline vitamin B12 deficiency

Homocysteine testing is considered investigational for all other indications.

Scientific Background and Reference Resources

Research has evaluated the clinical utility of homocysteine as a risk predictor of coronary artery disease (CAD) in the general population and as a modifiable risk factor for patients with CAD.

Homocysteine as a risk factor for CAD.

Several prospective studies have evaluated the relationship between homocysteine and cardiovascular disease in asymptomatic patients, but the data derived from these studies are inconclusive. For example, Folsom and colleagues identified all patients who developed coronary heart disease among an initial cohort of 15,792 patients who participated in the Atherosclerosis Risk in Communities (ARIC) trial. (1) The median follow-up time was 3.3 years. Plasma homocysteine was evaluated from the stored blood samples of the 232 patients plus a random sample of the rest of the cohort. While homocysteine was a significant univariate predictor of CAD, this association was not significant after adjusting for other cardiac risk factors in multivariate analysis. Similarly, Evans and colleagues identified 240 cases of nonfatal myocardial infarction (MI) or coronary death among a cohort of 12,866 men participating in the Multiple Risk Factor Intervention Trial (MRFIT). (2) Plasma homocysteine from stored blood samples from these patients plus 472 control patients were evaluated. With a follow-up ranging from 11 to 17 years, homocysteine levels did not appear to be an independent risk factor for coronary heart disease. In contrast, in a prospective study using similar methodology as the previously cited studies, Wald and colleagues reported that the initial stored plasma level of homocysteine was significantly higher among 229 men who ultimately died of ischemic heart disease compared to a control group of 1,126 men who were drawn from the original study of 21,520 men. (3) Also, Arnesen and colleagues found homocysteine was a risk factor for coronary heart disease based on their study of 122 patients who developed coronary heart disease from a sample of 21,826 men and women. (4)

For patients with known CAD, prospective data are more consistent in supporting the utility of homocysteine as a risk factor for future events. For example, Nygard and colleagues prospectively studied the plasma homocysteine levels in 587 patients with angiographically confirmed coronary artery disease. (5) After a median follow-

up of 4.6 years, the authors compared the initial homocysteine levels of the 64 patients (10.9%) who had died to those of the remaining 523 survivors. The authors reported a strong graded dose-response relationship between plasma homocysteine and mortality. Stubbs and colleagues evaluated the relationship between plasma homocysteine levels and cardiac events in 440 patients with acute coronary syndromes admitted to the hospital. (6) Plasma homocysteine levels at admission were not related to short-term outcomes at 28 days; however, in long-term follow-up, patients with homocysteine levels in the 2 highest quintiles had a 2.6-fold increase in the subsequent risk of a cardiac event.

Knekt and colleagues reported the outcomes at 13 years' follow-up of 3,471 middle-aged Finnish men, 884 of whom had known cardiovascular disease at baseline. (7) Using the homocysteine values from stored blood samples, they found no association between serum homocysteine concentration and the incidence of major coronary events (death from coronary heart disease or nonfatal MI) among men originally free of heart disease. However, a strong positive correlation was noted between homocysteine concentration and subsequent major coronary events in men with known cardiovascular disease at baseline.

A meta-analysis of 30 observational studies concluded that homocysteine was, in general, a modest independent risk factor for the occurrence of cardiovascular events and strokes. The association between homocysteine levels and CAD was much stronger in retrospective studies involving subjects diagnosed with vascular disease than in prospective studies of healthy individuals. (8)

Homocysteine levels as a modifiable risk factor.

Several limitations are involved in evaluating whether or not reducing homocysteine levels leads to reduced cardiovascular risk. First, improved prediction of risk does not by itself result in better health outcomes. Clinical trial evidence on the impact of intervening and modifying the risk factor is required. Also, to improve outcomes, clinicians must have the tools to translate this information into clinical practice. This process involves guidelines that incorporate emerging risk factors into existing risk prediction models that are demonstrated to more accurately classify patients into risk categories and that are accompanied by treatment guidelines that better target interventions toward patients who will benefit the most. Currently, no target levels exist for optimal homocysteine levels.

In addition, adherence to a diet meeting the recommended daily allowance (RDA) for folate intake, regardless of homocysteine and/or folate levels, could result in decreased levels of homocysteine. In 1996, the U.S. Food and Drug Administration (FDA) required that all enriched grain products be fortified with folic acid to reduce the risk of neural-tube defects in newborns. This fortification has been associated with a decrease in homocysteine concentration. (9) Trials of homocysteine-lowering therapy, therefore, should evaluate the utility of treatments that lower homocysteine levels beyond those achieved by these general public health measures.

Indirect evidence suggests that homocysteine lowering may have beneficial effects on cardiovascular disease. Homocysteine lowering has been associated with favorable alterations in some vascular disease surrogates, such as ultrasound-measured endothelial function and exercise electrocardiogram (ECG). (10, 11) Also, epidemiologic evidence suggests that folate fortification of grain may have had a

beneficial effect on the incidence of cardiovascular disease. (12) Since fortification has been mandatory in the United States, an increase in serum folate levels and a corresponding decrease in serum homocysteine levels have been observed. During this same time period, an acceleration in the decline of stroke in the United States has been noted, a phenomenon that has not been seen in the United Kingdom, where fortification of grain with folate is not mandated. This indirect evidence, however, is not definitive in determining whether lowering homocysteine improves cardiovascular outcomes.

Numerous randomized, controlled trials have now been published that provide direct evidence on the benefit of vitamin therapy to reduce homocysteine and prevent cardiovascular events. These trials primarily included patients with pre-existing cardiovascular disease or patients at high risk for cardiovascular disease. Among the largest of these trials to date are the Heart Outcomes Prevention Evaluation Trial 2 (HOPE-2) (13), the Norwegian Vitamin Trial (NORVIT) (14), the Western Norway B Vitamin Intervention Trial (WENBIT) (15), the Vitamin Intervention for Stroke Prevention (VISP) trial (16), and the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS). (17)

The HOPE-2 (13) included 5,522 patients with pre-existing vascular disease. Patients were randomized to treatment with a regimen of folate, vitamin B6, and vitamin B12 or placebo and followed up for an average of approximately 5 years. There were no significant differences in the composite outcome of cardiovascular death, MI, or stroke (relative risk [RR] 0.95; 95% CI: 0.84–1.07). However, there was a significant decrease in the risk of stroke for patients in the treatment group (RR 0.75; 95% CI: 0.59-0.97, p=0.03). For the secondary outcome of hospitalization for unstable angina, an increased risk was reported for the treatment group (RR 1.24; 95% CI: 1.04-1.49, p=0.02).

The NORVIT (14) enrolled 3,749 patients with a recent MI and randomized patients to combinations of folate and/or B vitamins. Patients were followed up for a mean of 3.3 years for the primary outcome, which was a composite of recurrent MI, stroke, and sudden cardiac death. For patients assigned to the active treatment groups, no significant reductions were noted in any of the primary or secondary outcomes. For patients assigned to the combined folate/vitamin B6/vitamin B12 group, an increased risk that was marginally significant (RR 1.22; 95% CI: 1.00–1.50, p=0.05) was observed for the primary composite outcome group.

A second randomized, controlled trial from Norway was published in 2008, the Western Norway B Vitamin Intervention Trial (WENBIT). (15) A total of 3,096 participants referred for coronary angiography were randomized to B vitamins alone, B vitamins plus folate, or placebo. Patients were followed up for a mean of 3.2 years with a primary composite outcome of all-cause mortality, MI, stroke, and hospitalization for unstable angina. There were no significant reductions in the incidence of the primary outcome for any of the treatment groups. For patients treated with a combination of folate/vitamin B6/vitamin B12, the hazard ratio for the primary outcome was 0.90 (95% CI: 0.74–1.09, p=0.28). Stroke was reduced for patients treated with folate versus those not treated with folate, but this difference did not reach statistical significance (HR 0.72; 95% CI: 0.44-1.17, p=0.19).

The VISP (16) enrolled 3,680 patients with a prior history of ischemic stroke and randomized them to either a high dose or a low dose of folate, vitamin B6 and vitamin B12. There was no significant difference reported for the primary outcome,

risk of recurrent stroke, which was 9.2% in the high-dose group compared with 8.8% in the low-dose group. Similarly, there were no significant differences reported in the rate of cardiac outcomes between groups.

Another recently published large, randomized controlled trial was the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS). (17) This trial randomized 5,442 women with a history of cardiovascular disease or at least three cardiovascular disease risk factors to a combination of folate, vitamin B6, and vitamin B12, with a mean follow-up of 7.3 years. The primary outcome was a composite of cardiovascular mortality, MI, stroke, and myocardial revascularization. There was no significant reduction in the primary outcome for the treatment group (RR 1.03; 95% CI: 0.90–1.13, p=0.65). There were also no significant reductions in risk for the individual endpoints, including stroke.

Several meta-analyses have been published that synthesize the available randomized controlled trial evidence on this question. (18-20) Bazzano and colleagues (18) included nearly 17,000 subjects from 12 studies. Pooled results did not reveal a significant decrease in cardiovascular disease (RR 0.95; 95% CI: 0.88–1.03) or all-cause mortality (RR 0.96; 95% CI: 0.88–1.04). The authors concluded that folic acid supplementation does not reduce the risk of cardiovascular events and that clinicians should focus their energies on proven cardiovascular risk reduction strategies such as smoking cessation, control of hypertension, and lipid-lowering therapies. Wald and colleagues (19) synthesized data from 7 studies of over 15,000 subjects and reported a similar RR for the outcome of ischemic heart disease (RR 0.98; 95% CI: 0.78–1.05). However, these authors concluded that the weight of observational and genetic studies, combined with the possibility that the trials were underpowered to detect small changes in RR and were of insufficient duration, prevented concluding a null effect with certainty.

A third meta-analysis evaluated the impact of folic acid supplementation for the prevention of stroke. (20) This analysis included 8 randomized controlled trials and approximately 17,000 patients. For all studies, a significant reduction was reported in the risk of stroke associated with folic acid supplementation (RR 0.82; 95% CI: 0.68–1.00, p=0.045). On sensitivity analysis, the beneficial effect appeared to be concentrated in study populations in whom grain fortification was not present (RR 0.75; 95% CI: 0.62–0.91, p=0.003). In contrast, no significant benefit was observed for study populations in whom grain fortification was provided (RR 0.89; 95% CI: 0.55–1.42, p=0.62).

The American Heart Association does not recommend population-wide screening for homocysteine levels nor does it recommend routine supplementation with folate and/or B vitamins to reduce homocysteine levels. (21) The Association's statement suggests that measurement of plasma homocysteine may have some role in patients with a personal or family history consistent with premature cardiovascular disease and that those with levels above10.0 micromol/L would be advised to increase their intake of folic acid. However the outcomes of this treatment strategy have not been addressed in controlled trials.

Summary and Conclusions. Observational evidence generally supports the association of homocysteine levels with risk of cardiovascular disease, especially in patients with pre-existing vascular disease. In addition, some indirect evidence suggests that homocysteine lowering may have cardiovascular benefits. However, evidence from randomized controlled trials does not support the hypothesis that

lowering homocysteine levels by treatment with folate and/or B vitamins improves cardiovascular outcomes. Numerous large, randomized controlled trials are consistent in reporting that treatment with folic acid is ineffective in reducing cardiac events. For the outcome of stroke, the evidence is less conclusive, with some randomized controlled trials reporting a benefit and others reporting no benefit. A meta-analysis of the effect of treatment on prevention of stroke suggests that there may be an overall benefit, but that this benefit is concentrated within populations in whom fortification of grain with folate is not present.

Therefore, the utility of routine testing for homocysteine and intervention for patients with hyper-homocysteinemia is questionable. There is currently insufficient evidence to prompt reconsideration of the current policy, which remains unchanged.

References:

1. Folsom AR, Nieto FJ, McGovern PG et al. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 1998; 98(3):204-10.
2. Evans RW, Shaten BJ, Hempel JD et al. Homocyst(e)ine and risk of cardiovascular disease in the Multiple Risk Factor Intervention Trial. Arterioscler Thromb Vasc Biol 1997; 17(10):1947-53.
3. Wald NJ, Watt HC, Law MR et al. Homocysteine and ischemic heart disease: results of a prospective study of implications regarding prevention. Arch Intern Med 1998; 158(8):862-7.
4. Arnesen E, Refsum H, Bonaa KH et al. Serum total homocysteine and coronary heart disease. Int J Epidemiol 1995; 24(4):704-9.
5. Nygard O, Nordrehaug JE, Refsum H et al. Plasma homocysteine levels and mortality in patients with coronary artery disease. N Engl J Med 1997; 337(4):230-6.
6. Stubbs PJ, Al-Obaidi MK, Conroy RM et al. Effect of plasma homocysteine concentration on early and late events in patients with acute coronary syndromes. Circulation 2000; 102(6):605-10.
7. Knekt P, Reunanen A, Alfthan G et al. Hyperhomocystinemia: a risk factor or consequence of coronary heart disease? Arch Intern Med 2001; 161(13):1589-94.
8. The Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 2002; 288(16):2015-22.
9. Jacques PF, Selhub J, Bostom AG et al. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. N Engl J Med 1999; 340(19):1449-54.
10. Woo KS, Chook P, Chan LL et al. Long-term improvement in homocysteine levels and arterial endothelial function after 1-year folic acid supplementation. Am J Med 2002; 112(7):535-9.
11. Vermeulen EG, Stehouwer CD, Twisk JW et al. Effect of homocysteine-lowering treatment with folic acid plus vitamin B_6 on progression of subclinical atherosclerosis: a randomized, placebo-controlled trial. Lancet 2000; 355(9203):517-22.

12. Yang Q, Botto LD, Erickson JD et al. Improvement in stroke mortality in Canada and the United States, 1990-2002. Circulation 2006;113(10):1335-43.
13. Lonn E, Yusuf S, Arnold MJ et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006; 354(15):1567-77.
14. Bonaa KH, Njolstad I, Ueland PM et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006; 354(15):1578-88.
15. Ebbing M, Bleie O, Ueland PM et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography. JAMA 2008; 300(7):795-804.
16. Toole JF, Malinow MR, Chambless LE et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004; 291(5):565-75.
17. Albert CM, Cook NR, Gaziano JM et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease. JAMA 2008; 299(17):2027-36.
18. . Bazzano LA , Reynolds K , Holder KN et al. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. JAMA 2006; 296(22):2720-6.
19. Wald DS, Wald NJ, Morris JK et al. Folic acid, homocysteine, and cardiovascular disease: judging causality in the face of inconclusive trial evidence. BMJ 2006; 333(7578):1114-7.
20. Wang X, Qin X, Demirtas H et al. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. Lancet 2007; 369(9576):1876-82.
21. Malinow MR, Bostom AG, Krauss RM et al. Homocyst(e)ine, diet and cardiovascular diseases: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. Circulation 1999; 99(1):178-92.

Administrative and Contractual Guidance

Benefit Determination Guidance

Benefits are subject to all terms, limitations and conditions of the subscriber contract.

For New England Health Plan (NEHP) members an approved referral authorization is required.

BlueCard/National Account Issues
Determination of homocysteine may be included as a component of a comprehensive cardiovascular risk assessment offered by reference laboratories. Comprehensive risk assessment may include evaluation of small low-density lipoproteins, subclassification of high-density lipoproteins, evaluation of apolipoprotein E genotype or phenotype, total plasma homocysteine, apolipoprotein B, and lipoprotein A.

Benefits for FEP members may vary. Please consult the FEP Service Plan Brochure.

Coverage varies according to the member's group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through a self-funded (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member's plan documents or contact the customer service department.

Billing and Coding/Physician Documentation Information

Follow the links listed below for attachments, coding tables and instructions.

Attachment I- CPT code table
Attachment II- Eligible Diagnosis Codes

Audit Information

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

Policy Implementation/Update information

1/2011	New policy.
3/2014	ICD-10 remediation. Non covered diagnosis removed. Only covered diagnoses are listed. New and revised standard language added (document precedence, audit information).

Approved by BCBSVT Medical Directors Date Approved

Spencer Borden MD
Chair, Medical Policy Committee

Robert Wheeler MD
Chief Medical Officer

Attachment I
CPT code table

Code Type	Number	Description
The following codes will be considered as medically necessary when applicable criteria have been met.		
CPT	83090	Homocysteine
Type of Service		Laboratory
Place of Service		Outpatient

Attachment II
Click HERE for eligible diagnosis codes