2.04.23	Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disorders		
Original Policy Date:	October 30, 2015	**Effective Date:**	March 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 17

Policy Statement

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

II. Measurement of plasma levels of homocysteine is considered **investigational** in the screening, evaluation, and management of individuals with venous thromboembolism or risk of venous thromboembolism.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The following CPT code is specific to this test:

- 83090: Homocysteine

Description

Homocysteine is an amino acid that has been evaluated as a potential marker of cardiovascular disease (CVD) and as a potential risk marker for people with CVD and thrombotic disorders; the presence of this amino acid raises one's risk of developing a blood clot. The association between homocysteine-lowering interventions and the risk of CVD or thrombotic events has been examined.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Several of the homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA product code: LPS. Examples are listed in Table 1.

Table 1. Homocysteine Test Systems

Assay	Laboratory	Approval Date
Homocysteine Enzymatic Assay	Roche Diagnostics	2012
Diazyme Enzymatic Homocysteine Assay	Diazyme Laboratories	2012
A/C Automatic Enzymatic Hcy [Homocysteine] Assay	AntiCancer Inc.	2008
Teco Enzymatic Homocysteine Assay	Teco Diagnostics	2007

Rationale

Background

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.

Plasma levels of homocysteine have been actively researched as a risk factor for cardiovascular disease (CVD), 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 CVD. Subsequently, prospective epidemiologic studies were conducted to determine if an elevated plasma level of homocysteine was an independent risk factor for CVD and could be used to improve current risk prediction models. Several case-control studies have also suggested that elevated homocysteine is a risk factor for venous thromboembolism (VTE; pulmonary embolism, deep vein thrombosis).

Interest in homocysteine as a potentially modifiable risk factor has been stimulated by the epidemiologic finding that levels of homocysteine inversely correlate 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 CVD and thrombotic events. Therefore, homocysteine has a potential utility both as a risk predictor and as a target of treatment.

Determination of homocysteine concentration may be offered as a component of a comprehensive cardiovascular risk assessment that may include evaluation of small-density lipoproteins, subclassification of high-density lipoproteins, evaluation of lipoprotein (a), high-sensitivity C-reactive protein, and genotyping of apolipoprotein E. Determination of homocysteine concentration may also be offered as part of the risk assessment for patients at high-risk of VTE events or who have experienced idiopathic VTE, recurrent VTE, thrombosis occurring at a young age, or thrombosis at an unusual site.

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more

applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Homocysteine levels are known to be associated with risk of cardiovascular disease (CVD) and venous thromboembolism (VTE). This evidence review focuses on direct evidence for the clinical utility of homocysteine testing: the results of randomized controlled trials (RCTs) that used folic acid or vitamin supplementation in order to reduce the occurrence of cardiovascular (CV) events or thromboembolism - as testing has clinical utility only if it informs management decisions that improve health outcomes.

Cardiovascular Disease

Relationship Between Homocysteine Levels and Cardiovascular Disease

Studies have shown an association between homocysteine levels and the risk of CVD. One study analyzing nationally representative survey data found that adding homocysteine levels to the Framingham Risk Score (FRS) significantly improved risk prediction. [1,] Studies have also found a significant correlation between homocysteine levels in patients with known CVD and subsequent coronary events. Overall, the available evidence has suggested that homocysteine levels are associated with increased risk of a variety of CV disorders and outcomes among patients with existing CVD.

The Homocysteine Studies Collaboration (2002) published a meta-analysis of observational studies evaluating the association between homocysteine concentration and risk of ischemic heart disease (IHD) or stroke.[2,] Thirty studies were identified that had individual patient data available; this included 18 retrospective studies and 13 prospective studies. In the prospective studies, blood for measuring homocysteine concentration was collected before the clinical onset of disease. The adjusted odds ratio (OR) of IHD associated with a 25% lower homocysteine level was 0.83 (95% confidence interval [CI], 0.77 to 0.89) in prospective studies, 0.67 (95% CI, 0.62 to 0.71) in retrospective studies using population controls, and 0.73 (95% CI, 0.64 to 0.83) in retrospectives studies with other controls. The adjusted OR of stroke associated with a 25% lower homocysteine level was 0.77 (95% CI, 0.66 to 0.90) in prospective studies, 0.86 (95% CI, 0.73 to 1.01) in retrospective studies with population controls, and 0.46 (95% CI, 0.30 to 0.70) in retrospective studies with other controls. The risk of IHD and stroke was significantly weaker in the prospective studies than in the retrospective studies, which may reflect biases in retrospective studies.

Representative studies on the association between homocysteine and various types of CVD, published after the Homocysteine Studies Collaboration meta-analysis, are described in Table 2.

Table 2. Select Individual Studies of Homocysteine and Cardiovascular Disease Risk

Study	Population	Outcomes	Major Findings (95% CI)
Shoamanesh et al (2016)[3,]	3224 adults from Framingham Offspring Cohort (community-dwelling sample)	Incident ischemic stroke	After adjusting for SBP, hypertension treatment, current smoking, diabetes, CVD, and atrial fibrillation, total homocysteine associated with incident ischemic stroke: • HR, 1.20 (1.01 to 1.43)
Han et al (2015)[4,]	5488 individuals with follow-up from a population-based prospective cohort study of 5935 hypertensive individuals	Incident ischemic stroke	• Homocysteine levels ≥15 µmol/L associated with higher ischemic stroke rates: HR, 2.18 (1.65 to 2.89) • Among 501 subjects who took folic acid supplementation,

Study	Population	Outcomes	Major Findings (95% CI)
			plasma homocysteine levels declined an average 6.7 µmol/L (clinical outcomes not reported separately)
Shi et al (2015)[5,]	3799 adults with ischemic stroke enrolled in a single hospital in China	Poststroke mortality	Among 223 patients who died during follow-up, those with highest 3rd and 4th quartiles of homocysteine had higher risk of stroke death, after adjusting for confounding variables: • 3rd vs. 1st quartile: adjusted HR, 2.27 (1.06 to 4.86; p=.029) • 4th vs. 1st quartile: adjusted HR, 2.15 (1.01 to 4.63; p=.049)
Wang et al (2014)[6,]	5935 individuals with hypertension enrolled in a population-based prospective cohort study	• Incident ischemic stroke • CHD	• Homocysteine levels ≥30 µmol/L (vs. <15 µmol/L) associated with higher ischemic stroke rates after adjusting for ischemic stroke risk factors: OR, 2.86 (1.72 to 4.75) • Homocysteine levels ≥30 µmol/L (vs. <15 µmol/L) not associated with CHD
Park et al (2010)[7,]	6371 individuals ages 40-79 y without history of MI, stroke, or PAD; 3860 (61%) with homocysteine level available	10-y CVD risk based on FRS: • Low risk (n=2527) • Intermediate risk (n=3336) • High risk (n=508)	• Homocysteine levels at ³85th percentile associated with high FRS: OR, 2.1 (1.48 to 3.01) • Homocysteine levels at 85th percentile not significantly associated with intermediate FRS: OR, 1.11 (0.89 to 1.38)

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; FRS : Framingham Risk Score; HR: hazard ratio; MI: myocardial infarction; OR: odds ratio; PAD: peripheral arterial disease; SBP: systolic blood pressure.

Clinical Context and Test Purpose

The purpose of testing homocysteine levels in asymptomatic individuals at risk of CVD or in individuals who have CVD is to inform management decisions such as whether to lower homocysteine levels.

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

Populations

The relevant population of interest are individuals who are asymptomatic with the risk of CVD and those who have CVD.

Interventions

The therapy being considered is homocysteine testing.

Comparators

The following practice is currently being used to manage those at risk of CVD and those with CVD: routine care without homocysteine testing, and therefore no supplementation for homocysteine lowering.

Outcomes

The general outcomes of interest are changes in disease status and morbid events attributable to CVD, including CV death, stroke, and myocardial infarction (MI). The time frame for an outcome varies from 1 to 2 years, for assessment of hypertension or vascular changes, to 3 or more years, for assessment of CV death, coronary artery disease (CAD), or stroke events.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess the clinical utility of homocysteine testing in the management of CVD, studies should demonstrate how test results impact treatment decisions and overall patient management and lead to an improvement in the net health outcome;
- Studies examining the use of homocysteine lowering therapy with folic acid or vitamin B supplementation were included;
- Systematic reviews were sought, and when not available, RCTs were included.

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

A Cochrane systematic review (2017[8,] ; originally published in 2009 and updated in 2013 [9,] and 2015 [10,]) evaluated the effectiveness of homocysteine-lowering interventions for preventing CV events, including both MI and stroke, in patients with and without pre-existing CVD. Reviewers included RCTs assessing the effects of homocysteine-lowering interventions for preventing CV events with at least 1 year of follow-up and considered MI and stroke as the primary outcomes. Fifteen trials (N=71,422) met eligibility criteria. Eleven studies included more than 1000 participants. Ten studies used placebo controls, 2 used usual care controls, and 2 compared doses of homocysteine-lowering therapy. In a pooled analysis of 12 trials, there was no statistically significant difference in nonfatal or fatal MI between intervention and control groups (relative risk [RR], 1.02; 95% CI, 0.95 to 1.10). In a pooled analysis of 10 studies, there was a statistically significant difference between groups in the rate of nonfatal or fatal stroke favoring homocysteine lowering over placebo (RR, 0.90; 95% CI, 0.82 to 0.99). This is a notable change from the previous 2015 Cochrane systematic review, which did not find a significant difference in the rate of nonfatal or fatal stroke based on 9 trials (RR, 0.91; 95% CI, 0.82 to 1.00). Nine of the 10 trials in this analysis included patients with a history of CVD, while only 1 trial included patients without CVD. Authors considered this result to be weak, due to the upper bound of the CI and low documented stroke rate in studies. There was also no significant mortality benefit in groups assigned to homocysteine-lowering therapy compared to placebo. For mortality of any cause, the RR was 1.01 (95% CI, 0.96 to 1.06) in a meta-analysis of 11 trials. Included RCTs were assessed as having low risk of attrition bias and selective outcome reporting bias.

A meta-analysis by Park et al (2016) of RCTs evaluated homocysteine-lowering therapy with B vitamins for reducing the risk of subsequent stroke among high CVD risk individuals who were not taking antiplatelet medications.[11,] Reviewers included 3 trials from 1966 to April 2015 that had at least 1 year of follow-up with stroke as the primary outcome: The Vitamin Intervention for Stroke Prevention trial (N=1773), the VITAmins TO Prevent Stroke trial (N=1463), and the Heart Outcomes Prevention Evaluation (HOPE) 2 trial (N=1407). There was no evidence of heterogeneity for the stroke outcome. Those taking vitamin B supplementation had a lower risk of recurrent stroke (hazard ratio [HR], 0.71; 95% CI, 0.58 to 0.88) compared with controls (low-dose supplementation or placebo). In

the VITAmins TO Prevent Stroke trial, participants not on antiplatelet therapy were more likely to be East Asian. In the HOPE-2 trial, the effect of supplementation on stroke was highest in those with hyperhomocysteinemia or residing in a country without food fortification. Therefore, it is not clear whether the effect of homocysteine-lowering therapy on stroke risk in those not on antiplatelets would apply to a U.S. population.

A meta-analysis by Yi et al (2014) included RCTs that compared folic acid supplementation (at least 5 mg/day for at least 4 weeks), without vitamin B supplementation, with placebo and evaluated the endothelial function and homocysteine levels as outcomes in patients with CAD.[12,] Six trials (N=377 subjects) were included. In the pooled analysis, folic acid supplementation was associated with increased flow-mediated dilation, a noninvasive, ultrasound-based method to assess vascular endothelial function (mean difference, 57.72 µm; 95% CI, 50.14 to 65.3 µm; p<.05). Folic acid supplementation was also associated with reduced plasma homocysteine concentration (mean difference, -3.66 µmol/L; 95% CI, -5.44 to -7.87 µmol/L; p<.05). For other measures of endothelial function, there was no significant change in the response to end-diastolic diameter, glyceryl-trinitrate diameter, heart rate, baseline, and peak hyperemic flow, or systolic and diastolic blood pressure between the folic acid and placebo groups.

Liu et al (2014) also reported the results of a meta-analysis of placebo-controlled randomized trials that evaluated the effect of homocysteine-lowering therapies on flow-mediated dilation in patients with CAD.[13,] Eight studies (N=611 subjects) were included; folic acid doses ranged from 400 to 10,000 µg/day. In the pooled analysis, folic acid supplementation was associated with improved flow-mediated dilation compared with placebo (standardized mean difference, 1.65; 95% CI, 1.12 to 2.17; p<.001), but there was significant heterogeneity across studies.

A meta-analysis by Huang et al (2012) assessed RCTs evaluating vitamin B supplementation in patients with preexisting vascular disease.[14,] This review had more lenient inclusion criteria because there was no limitation on study size or intervention duration. Nineteen trials (N=47,921 patients) were selected for the meta-analysis. In a pooled analysis of study data, reviewers found a statistically significant benefit of vitamin B supplementation on stroke (RR, 0.88; 95% CI, 0.82 to 0.95). Similar to the other meta-analyses, vitamin B supplementation did not have a statistically significant impact on other outcomes, including CHD, MI, and all-cause mortality. Given the more relaxed entry criteria, the meta-analysis might have included lower quality studies; reviewers did not present a formal analysis of trial quality.

Zhou et al (2011) conducted a systematic review of double-blind, placebo-controlled, randomized trials evaluating the impact of folic acid supplementation on CV outcomes.[15,] Interventions were included if they involved supplementation with vitamin B in addition to folic acid. Reviewers selected only trials that included at least 100 patients and had at least 6 months of follow-up. Of 66 articles retrieved, 16 trials with data on 44,841 patients met reviewers' inclusion criteria. In a meta-analysis of findings from 12 trials, folic acid supplementation did not have a significant effect on major CV events compared with placebo (RR, 0.98; 95% CI, 0.93 to 1.04). In addition, folic acid supplementation did not have a significant effect on individual outcomes including stroke (12 trials; RR, 0.89; 95% CI, 0.78 to 1.01), MI (11 trials; RR, 1.00; 95% CI, 0.93 to 1.07), or all-cause mortality (14 trials; RR, 1.00, 95% CI, 0.96 to 1.05).

Clarke et al (2011) published a meta-analysis of placebo-controlled, homocysteine-lowering, randomized trials.[16,] This meta-analysis selected studies that included at least 1000 participants and had at least 1 year of follow-up. Eight trials (N=37,485 individuals) met reviewers' inclusion criteria. In a pooled analysis of findings from the 8 trials, vitamin B supplementation did not have a significant effect on the risk of CHD events compared with placebo (RR, 1.01; 95% CI, 0.96 to 1.07). In addition, in pooled analyses of data from the 8 trials, vitamin B supplementation did not have a significant effect on stroke events (RR, 0.96; 95% CI, 0.87 to 1.07), cancer events (RR, 1.08; 95% CI, 0.99 to 1.17), or all-cause mortality (RR, 1.02; 95% CI, 0.97 to 1.07).

Randomized Controlled Trials

Representative RCTs evaluating homocysteine-lowering interventions are described next. Van Dijk et al (2015) reported on the results of the B-Vitamins for the PRevention Of Osteoporotic Fractures trial, an RCT comparing B vitamins (vitamin B_{12} 500 mg, folic acid 400 mg) with placebo for improving CV outcomes among elderly patients with hyperhomocysteinemia.[17,] The trial included 2929 subjects over age 65 years with elevated homocysteine levels (12 to 50 µmol/L) who were randomized to 2 years of B-vitamin therapy (n=1458) or placebo (n=1461). A random sample of participants (n=569) underwent baseline vascular measurements. Within the vascular subgroup, the aortic pulse pressure after 2 years of the intervention was significantly higher in the B-vitamin treatment group (49.6 mm Hg) than in the placebo group (47.2 mm Hg; p=.02). However, aortic-femoral pulse wave velocity and carotid intima-media thickness did not differ significantly between groups. In the vascular subgroup, serum homocysteine increased by 0.6 µmol/L in the placebo group but decreased by 3.6 µmol/L in the B-vitamin therapy group. In the entire study population, the treatment groups did not differ significantly in blood pressure or hypertension incidence, CV event incidence, or MI incidence. In a subgroup analysis, women in the treatment group experienced fewer CV events compared with women in the placebo group (OR, 0.33; 95% CI, 0.15 to 0.71).

In 2010, findings from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine in the U.K. were reported.[18,] A total of 12,064 adults with a history of MI were randomized to folic acid plus vitamin B_{12} or placebo. An additional eligibility criterion was blood cholesterol of at least 135 mg/dL if taking a statin or 174 mg/dL otherwise. Before randomization, patients participated in a run-in period to confirm adherence to treatment. (Patients were also randomized to receive different doses of simvastatin; those findings were not reported here.) After 3 to 4 years of follow-up, due to the low number of major coronary events in the treatment group, the steering committee (blinded to interim between-group outcomes) changed the primary outcome from major coronary events to major vascular events. This composite variable included nonfatal MI, death from CHD, fatal or nonfatal stroke, or any arterial revascularization. After a mean follow-up of 6.7 years, vitamin treatment was not associated with a statistically significant reduction in the primary outcome. The number of major vascular events was 1537 (25.5%) in the vitamin group and 1493 (24.8%) in the placebo group (RR, 1.04; 95% CI, 0.97 to 1.12). There were no significant differences in risk for any of the components of the composite outcome. In addition, death from all causes did not differ significantly between groups; there were 983 (16.3%) deaths in the vitamin group and 951 (15.8%) in the placebo group (RR, 1.04; 95% CI, 0.96 to 1.13).

The Heart Outcomes Prevention Evaluation (HOPE) 2 trial, which was reported by Lonn et al (2006), is the only trial included in the 2017 Cochrane review that showed a statistically significant difference in fatal and non-fatal stroke with homocysteine-lowering therapy. The trial included 5522 patients with preexisting vascular disease or diabetes.[19,] Patients were randomized to a regimen of folate, vitamin B_6, and vitamin B_{12} or placebo and followed for an average of 5 years. There were no significant differences in the composite outcome of CV death, MI, or stroke (RR, 0.95; 95% CI, 0.84 to 1.07). However, there was a significant decrease in the risk of stroke for patients in the treatment group compared to placebo (4% vs. 5.3%; RR, 0.75; 95% CI, 0.59 to 0.97; p=.03). Most strokes were classified as ischemic (71.7%) and nonfatal (77.9%), while 18.6% were documented as uncertain type (i.e., stroke was not confirmed by computed tomography or magnetic resonance imaging). No difference in transient ischemic attack was noted in the study. Additionally, results were not adjusted for the multiplicity of outcomes compared, increasing risk of type 1 error. For the secondary outcome of hospitalization for unstable angina, a significantly increased risk was reported for the treatment group (RR, 1.24; 95% CI, 1.04 to 1.49; p=.02).

The Norwegian Vitamin Trial (2006) enrolled 3749 patients with a recent MI who were randomized to combinations of folate and/or B vitamins.[20,] Patients were followed for a mean of 3.3 years for the primary outcome (a composite of recurrent MI, stroke, and sudden cardiac death). For patients assigned to the active treatment groups, no significant reductions were noted for any of the primary or secondary outcomes. For patients assigned to the combined folate/vitamin B_6/vitamin B_{12} group,

a marginally significant increased risk (RR, 1.22; 95% CI, 1.00 to 1.50; p=.05) was observed for the primary composite outcome group.

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 RCTs.

Vitamin B and folic acid supplementation are potential interventions that could lower homocysteine levels in patients with high homocysteine levels and improve health outcomes. However, public health measures are already in place that require 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 plasma homocysteine concentration in a population-representative adult sample.[21,] Trials evaluating the impact of homocysteine-lowering therapy on health outcomes should thus evaluate the utility of treatments that lower homocysteine levels beyond those achieved by general public health measures. In addition, clear homocysteine target levels need to be established to impact clinical practice.

Numerous RCTs and meta-analyses of these trials have provided evidence on the benefit of vitamin therapy to reduce homocysteine levels and prevent CV events.

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.

Section Summary: Cardiovascular Disease

Numerous large, placebo-controlled, randomized trials evaluated the impact of folic acid and vitamin B supplementation on the risk of CV events, including MI and stroke. A Cochrane Review of these RCTs reported that homocysteine-lowering interventions did not have a statistically significant effect on the rate of MI or all-cause mortality. A lower rate of stroke was reported with homocysteine-lowering therapy; however, the clinical significance of this is uncertain.

Venous Thromboembolic Disorders

Relationship Between Homocysteine Levels and Venous Thromboembolic Disorders

Several studies have examined the relationship between homocysteine levels and VTE. Various meta-analyses, primarily composed of observational studies, found a significant association between homocysteine levels and risk of VTE, though the association was imprecise.[22,23,24,] A meta-analysis published by Den Heijer et al (2005) including 24 retrospective studies (n=3289 patients) and 3 prospective studies (n=476 patients) published before July 2003 estimated that a 5 µmol/L higher total plasma homocysteine level was associated with a 27% (95% CI, 1% to 59%) higher risk of venous thrombosis in prospective studies and a 60% (95% CI, 10% to 134%) higher risk in retrospective studies.[22,] Additionally, a subsequent large prospective study found an increased risk of VTE in men with high homocysteine levels (OR, 2.17; 95% CI, 1.20 to 3.91); no association was found in women (OR, 1.00; 95% CI, 0.52 to 1.92).[25,]

Clinical Context and Test Purpose

The purpose of testing homocysteine levels in asymptomatic individuals at risk of VTE or of individuals who have VTE events is to inform management decisions such as whether to lower homocysteine levels.

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

Populations
The relevant populations of interest are individuals who are asymptomatic with risk of VTE and those who have had VTE events.

Interventions
The therapy being considered is homocysteine testing.

Comparators
The following practice is currently being used to manage those at risk of VTE and those who have had VTEs: routine care without homocysteine testing, and therefore no folic acid or vitamin B supplementation for homocysteine lowering. The comparator would ideally be in populations where the food supply is not fortified.

Outcomes
The general outcomes of interest are changes in disease status and morbid events associated with VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE).

The time frame for outcomes varies but it is expected to be 3 or more years for assessment of DVT or PE.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess the clinical utility of homocysteine testing in the management of CVD, studies should demonstrate how test results impact treatment decisions and overall patient management and lead to an improvement in the net health outcome;
- Studies examining the use of homocysteine lowering therapy with folic acid or vitamin B supplementation were included;
- Systematic reviews were sought, and when not available, RCTs were included.

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
Zhou et al (2012) published a systematic review including 2 observational studies and 3 RCTs on the association between B-group vitamins and VTE. [26,] The studies included an uncontrolled interventional study in patients with homocystinuria, an observational study of pregnant women, a trial with measured homocysteine levels as the primary outcome, a secondary analysis of the HOPE-2 trial, and a secondary prevention trial. Reviewers did not perform a meta-analysis due to heterogeneity in study designs and baseline homocysteine levels. The uncontrolled study in patients with homocystinuria and the study in pregnant women both found an association between supplementation and decreased risk of VTE. The trial with homocysteine levels as an outcome showed that supplementation with a multivitamin (folic acid 5 mg, vitamin B_{12} 0.4 mg, vitamin B_6 50 mg) reduced homocysteine levels in patients with recurrent VTE and in healthy volunteers. The 2 trials with VTE outcomes are detailed in the following section.

Randomized Controlled Trials
The Vitamins and Thrombosis RCT (2007) evaluated the effect of homocysteine-lowering by daily supplementation with B vitamins on the risk reduction of DVT and PE.[27,] Patients between 20 and 80 years of age with a first DVT or PE in the absence of major risk factors and a homocysteine concentration above the 75th percentile of a reference group were eligible (the hyperhomo-

cysteinemic group). The second group of patients with homocysteine below the 75th percentile of the reference group (called the normohomocysteinemic [placebo] group) were also enrolled. Patients were randomized to daily multivitamin supplementation with folic acid 5 mg, pyridoxine 50 mg, and cyanocobalamin 0.4 mg, or to a placebo. Follow-up continued for 2.5 years. The primary outcome was objectively diagnosed recurrent DVT or PE. A total of 701 patients were enrolled (360 in the hyperhomocysteinemic group, 341 in the normohomocysteinemic group). Of the 353 assigned to the vitamin group, 43 events were observed (54/1000 person-years). In the 348 assigned to the placebo group, 50 events were observed (64/1000 person-years). The HR was not statistically significant (HR, 0.84; 95% CI, 0.56 to 1.26). There was no statistically significant reduction in recurrent VTE in the 360 patients with baseline homocysteine levels above the 75th percentile (HR, 1.14; 95% CI, 0.65 to 1.98), or in the 341 patients with normal homocysteine levels (HR, 0.58; 95% CI, 0.31 to 1.07).

The HOPE-2 trial (2007) evaluated whether long-term supplementation with folic acid, vitamin B_6, and vitamin B_{12} aimed at lowering homocysteine levels would reduce the rates of major fatal and nonfatal CV events in patients with established CVD and/or diabetes.[28,] HOPE-2 was conducted at 145 clinical centers in 13 countries and enrolled 5522 patients aged 55 years or older with known CVD or diabetes and at least 1 other risk factor for vascular disease. Baseline information on previous VTE was not available. A secondary analysis from the HOPE-2 trial evaluated whether supplementation could reduce the risk of symptomatic VTE. The incidence of VTE occurred in 88 patients during a mean 5-year follow-up. There was no effect of vitamin supplementation on rates of VTE in the total population (HR, 1.01; 95% CI, 0.66 to 1.53) or in the 821 patients with baseline homocysteine levels in the highest quartile (>13.8 µmol/L) in the study (HR, 1.71; 95% CI, 0.48 to 6.06).

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 RCTs.

A systematic review of observational studies and RCTs have provided evidence relevant to the discussion of vitamin therapy to reduce homocysteine levels and prevent VTE.

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.

Section Summary: Venous Thromboembolic Disorders

A systematic review and a few placebo-controlled, randomized trials have evaluated the impact of folic acid and vitamin B supplementation on the risk of VTE. Homocysteine-lowering interventions did not have a statistically significant effect on the rate of VTE in patients with previous VTE or in patients unselected for previous VTE but with CVD. Based on available studies, there is insufficient evidence to conclude that supplementation to reduce homocysteine will reduce the risk of VTE.

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.

Cardiovascular Disease

National Institute for Health and Care Excellence

In 2023 , NICE updated its guidance on risk assessment and reduction of cardiovascular disease (CVD), including lipid modification.[29,] The guidance asserted that full formal risk assessments should use a combination of risk assessment tools as well as informed clinical judgment. Homocysteine testing was not mentioned.

American Heart Association and American Stroke Association

In 2014, the American Heart Association (AHA) and the American Stroke Association (ASA) issued joint guidelines on the primary prevention of stroke.[30,] These guidelines were endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Preventive Cardiovascular Nurses Association. The guidelines stated that patients with hyperhomocysteinemia may be treated with B-complex vitamins to prevent ischemic stroke, but that the effectiveness was not clearly established (class IIb; level of evidence B). In 2021, the AHA/ASA released a joint guideline on the prevention of stroke in patients with stroke and transient ischemic attack (TIA).[31,] The guideline stated that "in patients with ischemic stroke or TIA with hyperhomocysteinemia, supplementation with folate, vitamin B6, and vitamin B12 is not effective for preventing subsequent stroke".

American College of Cardiology and American Heart Association

In 2019, the American College of Cardiology (ACC) and the AHA issued a joint guideline on the primary prevention of CVD.[32,] The use of homocysteine was not mentioned as a marker to guide prevention strategy.

In 2016, the ACC and AHA issued a joint guideline for the management of patients with lower extremity peripheral disease.[33,] The guideline recommended against the use of B-complex vitamin supplementation to lower homocysteine, since it did not show benefit in the HOPE-2 trial.

In 2013, the ACC and AHA issued joint guidelines on the assessment of atherosclerotic cardiovascular risk.[34,] These guidelines were endorsed by 6 medical specialty associations. The guidelines developed multivariable equations to estimate age- and race-specific arteriosclerotic cardiovascular risk. The equations included age, total and high-density cholesterol levels, systolic blood pressure, antihypertensive treatment use, diabetes history, and current smoking status. The use of homocysteine screening for assessing the atherosclerotic cardiovascular risk was not considered in these guidelines.

National Academy of Clinical Biochemistry

In 2009, the National Academy of Clinical Biochemistry published guidelines on biomarkers for primary prevention of CVD.[35,] The Academy concluded that while homocysteine is a modest independent CVD risk factor, homocysteine screening for primary prevention and assessment in healthy individuals was unwarranted.

Venous Thromboembolism

Agency for Healthcare Research and Quality

In 2016, the Agency for Healthcare Research and Quality issued guidelines for effective quality improvement in preventing hospital-associated venous thromboembolism.[36,] Content for this guidance was last reviewed in March 2023. The venous thromboembolism prevention protocol recommended a venous thromboembolism risk assessment, a bleeding risk assessment, and clinical decision support on prophylactic choices. Homocysteine testing was not mentioned in these guidelines.

National Institute for Health and Care Excellence

The NICE (2018; updated in 2019) issued guidance on reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism.[37,] Homocysteine testing was not mentioned in this guidance.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2018) issued a recommendation on the assessment of CVD risk with nontraditional risk factors.[38,] Homocysteine levels were not mentioned in this recommendation.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT00671346	Combined Analyses and Long-term Follow-up in the Two Norwegian Homocysteine Lowering B-Vitamin Trials NORVIT and WENBIT	6839	Jan 2021 (unknown status)
NCT03122002	A Prospective Cohort Study of Predictors and Prognostic Factors on the Acute Ischemic Stroke	1200	Dec 2022 (terminated)

NCT: national clinical trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	83090	Homocysteine
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/30/2015	Policy title change from Coronary Heart Disease (CHD) - Assessment of Emerging Risk Factors Policy revision without position change BCBSA Medical Policy adoption
03/01/2016	Policy revision without position change
02/01/2017	Policy title change from Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease Policy revision with position change
02/01/2018	Policy revision without position change
02/01/2019	Policy revision without position change
03/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2024	Policy reactivated. Previously archived from 09/01/2020 to 02/29/2024.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an

authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disorders 2.04.23** **Policy Statement:** I. Measurement of plasma levels of homocysteine is considered **investigational** in the screening, evaluation, and management of individuals for cardiovascular disease. II. Measurement of plasma levels of homocysteine is considered **investigational** in the screening, evaluation, and management of individuals with venous thromboembolism or risk of venous thromboembolism.