Homocysteine Testing
Corporate Medical Policy

Description

Homocysteine is an amino acid that has been evaluated as a potential marker of cardiovascular disease (CVD) and increased risk of thrombosis in the general population and as a potential risk marker for people with CVD and thrombotic disorders. The association between homocysteine-lowering interventions and risk of CVD or thrombotic events has also been examined.

For individuals who are asymptomatic with risk of CVD or who have CVD who receive homocysteine testing, the evidence includes observational studies and randomized controlled trials (RCTs) of homocysteine-lowering interventions. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and CVD risk, especially in patients with preexisting vascular disease. However, evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins improves cardiovascular outcomes. Numerous large RCTs and meta-analyses of these trials have consistently reported that homocysteine-lowering treatment is ineffective in reducing major cardiovascular events. One systematic review of a subgroup analysis from 3 RCTs of patients not on antiplatelets at baseline found that homocysteine-lowering treatment reduced the risk of stroke in that group. However, replication of this effect in countries with grain enriched with folic acid would be needed. Given the large amount of evidence from placebo-controlled RCTs that homocysteine-lowering interventions do not improve health outcomes, it is unlikely that routine homocysteine testing has the potential to change management that improves health outcomes. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who are asymptomatic with risk of venous thromboembolism (VTE) or who have experienced VTE events who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. Relevant outcomes
are test accuracy and validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and VTE risk, although the association was limited to men in the largest prospective study. However, evidence from RCTs evaluating homocysteine-lower interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces risk of VTE. Only 1 RCT was designed to test for VTE as a primary outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

The objective of this evidence review is to examine whether homocysteine testing in asymptomatic patients at risk of cardiovascular disease or venous thromboembolism or in patients who have cardiovascular disease or previous venous thromboembolism improves health outcomes.

Policy

Coding Information
Click the links below for attachments, coding tables & instructions.
Attachment I- CPT® code table
Attachment II- ICD-10 code table

When a service may be considered medically necessary

Measurement of plasma levels of homocysteine are considered medically necessary for the following indications:

- Assessment of borderline vitamin B-12 deficiency when the results of homocysteine testing will impact the members treatment plan; OR
- Assessment of homocystinuria caused by cystationine beta synthase deficiency (Note: for newborn screening, measurements of plasma homocysteine/total homocysteine are performed only when hyper-methioninemia has been confirmed; OR
- Assessment of idiopathic venous thrombo-embolism, recurrent venous thrombo-embolism, thrombosis occurring prior to age 45, or thrombosis at an usual site; OR
- Recurrent pregnancy loss once all other indications have been ruled out.

When a service is considered not medically necessary

Measurement of plasma levels of homocysteine are considered not medically necessary in the screening, evaluation, and management of patients with cardiovascular disease and all other indications not mentioned within this policy.

When a service is considered investigational

Measurement of plasma levels of homocysteine is considered investigational in the screening, evaluation, and management of patients with venous thromboembolism or risk of venous thromboembolism for all indications other than those listed above.
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. 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 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 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 CVD and thrombotic events. Therefore, homocysteine has 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, sub-classification of high-density lipoproteins, evaluation of lipoprotein (A), high-sensitivity C-reactive protein, and genotyping of apolipoprotein. Determination of homocysteine concentration may also be offered as part of 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.

Rationale/Scientific Background

This evidence review was originally created in May 2001 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 10, 2016. Following is a summary of the key literature to date.

Homocysteine testing can be evaluated in a similar framework as other novel cardiac risk factors. There are several conditions that must be met for a cardiovascular risk factor to demonstrate clinical utility. A 2002 TEC Assessment summarized 3 steps necessary for clinical utility:

- Standardization of measurement of the risk factor.
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor contributes independently to risk assessment compared with established risk factors.
- Determination of how the novel risk factor will be used in the management of the patient, compared with standard methods of assessing risk, and whether any
subsequent changes in patient management result in an improvement in patient outcomes.

Analytic Validity
The U.S. Food and Drug Administration have cleared commercially available kits for measuring homocysteine.

CARDIOVASCULAR DISEASE

Clinical Validity of Homocysteine and Cardiovascular Disease Risk Tests
In 2002, the Homocysteine Studies Collaboration published a meta-analysis of observational studies evaluating the association between homocysteine concentration and risk of ischemic heart disease (IHD) or stroke. A total of 30 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 ischemic heart disease 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 retrospective 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 the retrospective studies, which may reflect biases in retrospective studies.

Subsequent meta-analyses of observational studies have found significant associations between homocysteine and morbidity and mortality, including a 2015 meta-analysis of 12 studies, which found increased coronary artery disease (CAD), cardiovascular, and all-cause mortality with higher homocysteine levels.

Among the prospective studies was one by Folsom et al that identified patients who developed coronary heart disease (CHD) among an initial cohort of 15,792 patients participating in the Atherosclerosis Risk in Communities (ARIC) trial. 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. Another prospective study was published by Evans et al. The investigators 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). 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 CHD. In contrast, in a nested case-control study derived from a prospective cohort study of 21,520 men enrolled in the British United Provident Study, Wald et al reported that the initial stored plasma level of homocysteine was significantly higher among 229 men who ultimately died of IHD compared with a control group of 1126 men who did not die of IHD and did not have a history of IHD.
For patients with known cardiovascular disease (CVD), prospective data more consistently demonstrate that homocysteine is a risk factor for future events. In 1997, for example, Nygard et al reported on a prospective study of the plasma homocysteine levels in 587 patients with angiographically confirmed CAD. 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 with those of the remaining 523 survivors. The authors reported a strong graded dose-response relationship between plasma homocysteine and mortality. In addition, Knekt et al reported the outcomes at 13-year follow-up for 3471 middle-aged Finnish men, 884 of whom had known CVD at baseline. Using the homocysteine values from stored blood samples, a strong positive correlation was noted between homocysteine concentration and subsequent major coronary events in men with known CVD at baseline. However, they found no association between serum homocysteine concentration and the incidence of major coronary events (death from CHD or nonfatal MI) among men originally free of heart disease.

Since publication of the Homocysteine Studies Collaboration meta-analysis, a number of studies have reported on the association between homocysteine and CVD. In 2010, Park et al published an analysis of data from a large nationally representative survey of U.S. residents. The analysis was restricted to the 6371 individuals aged 40 to 79 years who had no history of MI, stroke, peripheral artery disease, or stroke. The investigators stratified participants according to their estimated 10-year risk of CVD, using the Framingham risk score; low risk, less than 10% (n=2527), intermediate risk, 10% to 20% (n=3336), and high risk, greater than 20% (n=508). Information on homocysteine level was available for 3860 (61%) patients. There was a statistically significant association between elevated homocysteine levels (defined as at least the 85th percentile) and being categorized as having a high 10-year risk of CVD (OR=2.11; 95% CI, 1.48 to 3.01). The association between elevated homocysteine levels and intermediate cardiovascular risk was not significant (OR=1.11; 95% CI, 0.89 to 1.38). The survey was cross-sectional rather than prospective, limiting possible/potential conclusions about the predictive value of homocysteine levels.

In 2011, Veeranna et al published a post hoc analysis of national survey databases to evaluate whether adding homocysteine to the Framingham risk score model improves risk classification. The data were taken from the nationally representative surveys Multi-Ethnic Study of Atherosclerosis (MESA), which included subjects between the ages of 45 and 84 years with no prior history of CVD and the National Health and Nutrition Survey III (NHANES III), a sample of noninstitutionalized subjects. Homocysteine level was associated with CVD risk in both databases. In a receiver-operating curve analysis, the area under the curve (AUC) for predicting CHD events in the MESA database was 0.74 using the Framingham risk score and 0.76 when homocysteine level was added to the Framingham score. The improvement in risk prediction was statistically significant (p<0.001). The AUC for predicting CHD deaths in NHANES III was 0.84 using the Framingham risk score alone and 0.87 when homocysteine level was added to the Framingham score; this difference was statistically significant (p<0.001). Adding homocysteine to the Framingham model resulted in reclassification of 832 (12.9%) subjects in the MESA cohort and 1243 (18%) in the NHANES III cohort. This study does not address whether testing for homocysteine would improve health outcomes.

Section Summary: Clinical Validity of Homocysteine and Cardiovascular Disease Risk Tests
A meta-analysis of observational studies found a statistically significant moderate association between homocysteine levels and risk of CVD. Studies have also found a significant correlation between homocysteine levels in patients with known CVD and subsequent coronary events. One recent study analyzing nationally representative survey data found that adding homocysteine level to the Framingham risk score significantly improved risk prediction. Overall, the available evidence has suggested that homocysteine levels are associated with increased risk of a variety of cardiovascular disorders and outcomes among patients with existing CVD.

Clinical Utility of Homocysteine and Cardiovascular Disease Tests
Assessing whether use of homocysteine in clinical practice for the management of CVD has clinical utility requires demonstrating that identification of homocysteine levels leads to changes in patient management that improve patient outcomes.

Vitamin B and folic acid supplementation are potential interventions that could be used for patients with homocysteine levels to 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. 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 these general public health measures. In addition, clear target levels for homocysteine concentration would need to be established for translating information on homocysteine lowering into clinical practice.

Numerous randomized controlled trials (RCTs) have been published that provide evidence on the benefit of vitamin therapy to reduce homocysteine levels and prevent cardiovascular events. Moreover, several meta-analyses have synthesized the available RCT evidence on this question.

Systematic Reviews
A 2016 meta-analysis of RCTs evaluated homocysteine-lowering therapy with B vitamins for reducing risk of subsequent stroke among high CVD risk individuals who were not taking antiplatelet medications. 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 (VISP) trial, the VITamins TO Prevent Stroke (VITATOPS) trial, and the Heart Outcomes Prevention Evaluation (HOPE) 2 trial. The metaanalysis included 4643 participants (1773 in VISP, 1463 in VITATOPS, 1407 in HOPE-2) who were not taking antiplatelet agents at baseline. 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 to controls (low-dose supplementation or placebo). In VITATOPS, participants not on antiplatelet therapy were more likely to be East Asian. In HOPE-2, 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 if the effect of homocysteine-lowering therapy on stroke risk in those not on antiplatelets would apply to a U.S. population.
In 2015, a Cochrane systematic review, originally published in 2009 and updated in 2013, on the effectiveness of homocysteine-lowering interventions for preventing cardiovascular events, including both MI and stroke, was updated. The review included RCTs assessing the effects of homocysteine-lowering interventions for preventing cardiovascular events with at least 1 year of follow-up and considered MI and stroke as the primary outcomes. No new trials published since the last update were identified. Twelve trials with a total of 47,429 subjects met eligibility criteria. Nine of the studies included more than 1000 participants. Nine studies used placebo controls, 2 used usual care controls, and 1 compared high and low doses of homocysteine-lowering therapy. In a pooled analysis of 11 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 9 studies, there was no significant difference between groups in the rate of nonfatal or fatal stroke (RR=0.91; 95% CI, 0.82 to 1.00). There was also no significant mortality benefit in groups assigned to homocysteine-lowering therapy. For mortality of any cause, the relative risk was 1.01 (95% CI, 0.96 to 1.07) in a meta-analysis of data from 10 trials.

In 2011 Zhou et al conducted a systematic review of double-blind placebo-controlled RCTs evaluating the impact of folic acid supplementation on cardiovascular outcomes. Interventions were included whether or not they involved supplementation with vitamin B in addition to folic acid. The review was limited to trials that included at least 100 patients and had at least 6 months of follow-up. Of 66 articles retrieved for detailed inspection, 16 trials with data on 44,841 patients met the review’s inclusion criteria. In a meta-analysis of findings from 12 trials, folic acid supplementation was not found to have a significant effect on major cardiovascular 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).

Also in 2011, Clarke et al published a meta-analysis of placebo-controlled homocysteine-lowering RCTs. This meta-analysis was limited to studies that included at least 1000 participants and have at least 1 year of follow-up. A total of 8 trials with 37,485 individuals met the review’s inclusion criteria. In a pooled analysis of findings from the 8 trials, vitamin B supplementation did not have a significant effect on 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 was not found to 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).

A 2012 meta-analysis by Huang et al, included RCTs evaluating B vitamin supplementation in patients with preexisting vascular disease. This review had more lenient inclusion criteria, as there was no limitation on study size or intervention duration. A total of 19 trials with 47,921 patients were included in the meta-analysis. Unlike the other meta-analyses previously discussed, in a pooled analysis of study data, the authors 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 was not found to have a statistically significant impact on other outcomes, including CHD, MI, and all-cause mortality. Given the
more relaxed entry criteria, the meta-analysis may have included some lower-quality studies; the authors did not present a formal analysis of trial quality.

A 2014 meta-analysis included RCTs that compared folic acid supplementation (at least 5 mg/d for at least 4 weeks), without vitamin B supplementation, with placebo and evaluated endothelial function and homocysteine level as outcomes in patients with CAD. A total of 6 trials with 377 subjects were included. In pooled analysis, folic acid supplementation was associated with increased flow-mediated dilation (FMD), a noninvasive, ultrasound-based method to assess vascular endothelial function (mean difference (MD), 57.72 μm; 95% CI, 50.14 to 65.3; p<0.05). Folic acid supplementation was also associated with reduced plasma homocysteine concentration (MD = -3.66 μmol/L; 95% CI, -5.44 to -7.87; p<0.05). For other measures of endothelial function, there was no significant change in the response to end diastolic diameter, glyceral-trinitrate diameter, heart rate, baseline and peak hyperemic flow, and systolic and diastolic blood pressure between the folic acid and placebo groups.

Liu et al also reported results of a meta-analysis of placebo-controlled RCTs that evaluated the effect of homocysteine-lowering therapies on FMD in patients with CAD. A total of 8 studies with 611 subjects were included; folic acid doses ranged from 400 to 10,000 μg/d. In pooled analysis, folic acid supplementation was associated with improved FMD compared with placebo (standardized MD=1.65; 95% CI, 1.12 to 2.17; p<0.001), but there was significant heterogeneity across studies.

**Randomized Controlled Trials**

The HOPE-2 trial included 5522 patients with preexisting 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, myocardial infarction (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 (RR=0.75; 95% CI, 0.59 to 0.97; p=0.03). 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=0.02).

The NORVIT enrolled 3749 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 to 1.50; p=0.05) was observed for the primary composite outcome group.

In 2010, findings from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) in the U.K. were reported. A total of 12,064 adult patients with a history of MI were randomized to receive folic acid and vitamin B12 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 that they were adherent to treatment. (Patients were also randomized to receive different doses of
simvastatin; those findings are 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) decided to change 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 were 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).

Since the publication of the systematic reviews and meta-analyses described above, van Dijk et al reported results of the B-PROOF trial, an RCT comparing B vitamins (vitamin B12 500 mg and folic acid 400 mg) with placebo for improving cardiovascular outcomes among elderly patients with hyperhomocysteinemia. The study included 2929 subjects over age 65 with an elevated homocysteine level (12-50 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 intervention was significantly higher in the B vitamin treatment group than in the placebo group (49.6 mm Hg vs 47.2 mm Hg, p=0.02). 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 terms of blood pressure or hypertension incidence, cerebrovascular event incidence, or MI incidence. In subgroup analyses, among women, treatment group subjects had lower incidence of cerebrovascular events than placebo group subjects (OR=0.33; 95% CI, 0.15 to 0.71).

Section Summary: Cardiovascular Disease
Numerous large placebo-controlled RCTs have been published that evaluate the impact of folic acid/ vitamin B supplementation on risk of cardiovascular events, including MI and stroke. With few exceptions, meta-analyses of these RCTs have found that homocysteine-lowering interventions do not have a statistically significant effect on the rate of major cardiovascular events. Two meta-analyses of RCTs reported that homocysteine-lowering interventions are associated with improvements in a measure of vascular endothelial function, but it is uncertain whether these changes are associated with improved clinical outcomes.

VENOUS THROMBOEMBOLIC DISORDERS

Clinical Validity of Homocysteine and Venous Thromboembolism
Den Heijer et al (2005) published a meta-analysis of observational studies on the relation between homocysteine and risk of venous thrombosis. Twenty-four retrospective studies (3289 patients) and 3 prospective studies (476 patients) published before July 2003 were included. 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. Selected studies had varying cutoffs for high homocysteine and a mix of first-time and recurrent venous thromboembolism (VTE). Two earlier systematic reviews reached similar conclusions on the association between homocysteine and risk of VTE.

Several studies have examined the risk of VTE in patients with both homocysteinemia and an inherited thrombophilia (eg, factor V Leiden), with mixed results. Keijzer et al (2007) performed a meta-analysis of the interaction between factor V Leiden and hyperhomocysteinemia. In 5 observational studies (825 patients with venous thrombosis, 2109 controls), there was no evidence for additive or multiplicative interaction between factor V Leiden and hyperhomocysteinemia. The relative excess risk due to additive interaction was 1.77 (95% CI, -8.61 to 5.08) and multiplicative interaction term was 0.86 (95% CI, 0.35 to 2.14).

Following the systematic reviews, a case-cohort study from the large Norwegian Health Study of Nord-Trøndelag (HUNT2) prospectively investigated whether elevated plasma homocysteine levels before the event were associated with subsequent first VTE in a general population. VTE was identified in 505 patients, and 1458 age- and sex-matched controls were selected for the case-cohort study from the original cohort of 66,140 HUNT2 participants. Serum total homocysteine blood was collected between August 1995 and June 1997, a median of 33 months before the events. The odds ratio for VTE for homocysteine levels above versus below the 95th percentile was 1.50 (95% CI, 0.97 to 2.30). Results were similar after control for age, predisposing risk factors, or time to event. The association was limited to men (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). There was not a dose-response relation between VTE and homocysteine.

**Section Summary: Clinical Validity of Homocysteine and Venous Thromboembolism**

A meta-analysis of observational studies found a statistically significant moderate association between homocysteine levels and risk of VTE. However, a subsequent large prospective study found the risk to be only increased in men. The available evidence has suggested that homocysteine levels may be associated with increased risk of VTE in the general population.

**Clinical Utility of Homocysteine and VTE**

A systematic review of observational studies and 2 RCTs have provided evidence relevant to the discussion of vitamin therapy to reduce homocysteine levels and prevent VTE.

**Systematic Reviews**

Zhou et al (2012) published a systematic review of observational studies on the association between B-group vitamins and VTE. Five studies relating to the effects of B-group vitamins supplementation on VTE prevention were selected. The studies included 1 uncontrolled interventional study in patients with homocystinuria, 1 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 varying study designs and different 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 B12 0.4 mg, vitamin B6 50 mg) reduced homocysteine levels in patients with recurrent VTE and in healthy volunteers. The 2 trials with VTE outcomes are described in more detail in the following section.

**Randomized Controlled Trials**

The Vitamins and Thrombosis (VITRO) RCT (2007) evaluated the effect of homocysteine lowering by daily supplementation with B vitamins on the risk reduction of deep vein thrombosis (DVT) and pulmonary embolism (PE). 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 hyperhomocysteinemic group). A second group of patients with a homocysteine below the 75th percentile of the reference group (called the normohomocysteinemic group) were also enrolled. Patients were randomized to daily multivitamin supplementation of folic acid 5 mg, pyridoxine 50 mg, plus 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 [placebo] 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 hazard ratio did not differ statistically significantly from 1 (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 evaluated whether long-term supplementation with folic acid, vitamin B6, and vitamin B12 aimed at homocysteine reduction would reduce the rates of major fatal and nonfatal cardiovascular events in patients with established CVD and/or diabetes. HOPE-2 was conducted at 145 clinical centers in 13 countries and enrolled 5522 patients 55 years of age 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 risk of symptomatic VTE. 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).

**Section Summary: Clinical Utility of Homocysteine and VTE**

Two placebo-controlled RCTs have evaluated the impact of folic acid and vitamin B supplementation on 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 these trials, there is insufficient evidence to conclude that supplementation to reduce homocysteine will reduce risk of VTE.

**SUMMARY OF EVIDENCE**

For individuals who are asymptomatic with risk of cardiovascular disease (CVD) or who have CVD who receive homocysteine testing, the evidence includes observational studies and randomized controlled trials (RCTs) of homocysteine-lowering interventions. Relevant
outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and CVD risk, especially in patients with preexisting vascular disease. However, evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins improves cardiovascular outcomes. Numerous large RCTs and meta-analyses of these trials have consistently reported that homocysteine-lowering treatment is ineffective in reducing major cardiovascular events. One systematic review of a subgroup analysis from 3 RCTs of patients not on antiplatelets at baseline found that homocysteine-lowering treatment reduced the risk of stroke in that group. However, replication of this effect in countries with grain enriched with folic acid would be needed. Given the large amount of evidence from placebo-controlled RCTs that homocysteine-lowering interventions do not improve health outcomes, it is unlikely that routine homocysteine testing has the potential to change management that improves health outcomes. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who are asymptomatic with risk of venous thromboembolism (VTE) or who have experienced VTE events who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and VTE risk, although the association was limited to men in the largest prospective study. However, evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces risk of VTE. Only 1 RCT was designed to test for VTE as a primary outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION - PRACTICE GUIDELINES AND POSITION STATEMENTS
Cardiovascular Disease

National Institute for Health and Care Excellence
In 2016, the National Institute for Health and Care Excellence updated its guidance on risk assessment and reduction of cardiovascular disease (CVD), including lipid modification. The guidance asserts that full formal risk assessments should use a combination of risk assessment tools as well as informed clinical judgment. Homocysteine testing is not mentioned.

American Heart Association and American Stroke Association
In 2014, the American Heart Association and the American Stroke Association issued guidelines on the primary prevention of stroke. 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 is not clearly established (class IIb; level of evidence B).

American College of Cardiology and American Heart Association
In 2013, the American College of Cardiology and the American Heart Association issued guidelines on the assessment of arteriosclerotic cardiovascular risk (ASCVD). These guidelines were endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Society for Preventive Cardiology, American Society of Hypertension, Association of Black Cardiologists, National Lipid Association, Preventive Cardiovascular Nurses Association, and Women Heart: The National Coalition for Women with Heart Disease. The guidelines developed multivariable equations to estimate age- and race specific ASCVD 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 risk of ASCVD was not considered in these guidelines.

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

**Thromboembolism**

Agency for Healthcare Research and Quality
In 2016, the Agency for Healthcare Research and Quality (AHRQ) issued guidelines for effective quality improvement on preventing hospital-associated venous thromboembolism (VTE). The VTE prevention protocol recommended involves a VTE risk assessment, a bleeding risk assessment, and a clinical decision support on prophylactic choices. Homocysteine testing was not mentioned in these guidelines.

National Institute for Health and Care Excellence
In 2015, the National Institute for Health and Care Excellence updated its guidance on VTE in adults admitted to hospital. This guidance recommended that all patients be evaluated for VTE risk on hospital admission. Homocysteine testing was not mentioned in this guidance.

U.S. Preventive Services Task Force Recommendations
In 2009, the U.S. Preventive Services Task Force issued a recommendation statement that the evidence is insufficient (1 statement) to assess the benefits and harms of using nontraditional risk factors to screen asymptomatic adults with no history of coronary heart disease (CHD) to prevent CHD events. Homocysteine was one of the nontraditional risk factors considered in the recommendation. The recommendation statements are currently being updated.

**Regulatory status**

Several 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 below.

**Homocysteine Test Systems**

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Cleared</th>
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</thead>
</table>

Page 13 of 19
Medical Policy Number: UM.DIAG.02
### Homocysteine Enzymatic Assays

<table>
<thead>
<tr>
<th>Assay Description</th>
<th>Manufacturer</th>
<th>Year</th>
</tr>
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<tbody>
<tr>
<td>Homocysteine Enzymatic Assay</td>
<td>Roche Diagnostics</td>
<td>2012</td>
</tr>
<tr>
<td>Diazyme Enzymatic Homocysteine Assay</td>
<td>Diazyme Laboratories</td>
<td>2012</td>
</tr>
</tbody>
</table>

### Reference Resources

7. Park CS, Ihm SH, Yoo KD, et al. Relation between C-reactive protein, homocysteine levels, fibrinogen, and lipoprotein levels and leukocyte and platelet counts, and 10-year risk for cardiovascular disease among healthy adults in the USA. Am J Cardiol. May 1 2010;105(9):1284-1288. PMID 20403480


29. Study of the Effectiveness of Additional Reductions in Cholesterol Homocysteine Collaborative Group, Armitage JM, Bowman L, et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial

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, or employer’s benefit plan if an ASO group, 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/employer benefit plan language, the member’s contract/employer benefit plan language takes precedence.

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.

Administrative and Contractual Guidance

Benefit Determination Guidance

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member’s benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member’s benefit.

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 an Administrative Services Only (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member’s employer benefit plan documents or contact the customer service department. Language in the
employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>1/2011</td>
<td>New policy</td>
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<tr>
<td>6/2015</td>
<td>Adoption of BCBSA policy# 2.04.23. Approved by MPC on 4/13/15</td>
</tr>
<tr>
<td>06/2017</td>
<td>Medical policy name changed. Policy updated with literature review through October 10, 2016. Updated references based on BCBSA policy #2.04.23. Updated DX list. Title changed to “Homocysteine Testing”. Added medically necessary criteria/section, changed CVD from investigational to not medically necessary. Added investigational for homocysteine measurement in the evaluation of venous thromboembolic disease.</td>
</tr>
</tbody>
</table>

Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

Approved by BCBSVT Medical Directors  Date Approved

Gabrielle Bercy-Roberson, MD, MPH, MBA  
Senior Medical Director  
Chair, Health Policy Committee

Joshua Plavin, MD, MPH, MBA  
Chief Medical Officer

Attachment I  
CPT® Code Table

<table>
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<tr>
<th>Code Type</th>
<th>Number</th>
<th>Description</th>
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<tr>
<td>The following codes may be considered as medically necessary when applicable criteria have been met.</td>
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CPT 83090  Homocysteine  Refer to ICD 10 table below
## ICD-10 Code Table

<table>
<thead>
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<th>Description</th>
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<td>The following ICD 10 codes will be considered medically necessary when applicable criteria have been met.</td>
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<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>D51.0-D51.9</td>
<td>Vitamin B12 deficiency anemia</td>
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<tr>
<td>D81.818</td>
<td>Other biotin-dependent carboxylase deficiency</td>
</tr>
<tr>
<td>D81.819</td>
<td>Biotin-dependent carboxylase deficiency, unspecified</td>
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<tr>
<td>E53.8</td>
<td>Deficiency of other specified B group vitamins</td>
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<tr>
<td>E72.10-E72.11, E72.19</td>
<td>Disturbances of Sulphur-bearing amino acid metabolism {not covered for management of 5, 10-methylenetetrahydrofolate reductase (MTFR) abnormalities} Homocystinuria (Cystathionine synthase deficiency)</td>
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<tr>
<td>I26.01-I26.99</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>I81</td>
<td>Portal vein thrombosis</td>
</tr>
<tr>
<td>N96</td>
<td>Recurrent pregnancy loss</td>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
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<td>The following ICD-10 codes will be considered investigational</td>
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<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>I82.210-I82.91</td>
<td>Other venous embolism and thrombosis code range</td>
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</table>

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>The following ICD-10 codes will be considered not medically necessary as well as all other ICD-10 codes not classified as medically necessary or investigational within this medical policy.</td>
<td></td>
</tr>
<tr>
<td>I25.10-I25.119</td>
<td>Atherosclerotic heart disease of native coronary artery</td>
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<td>----------------</td>
<td>------------------------------------------------------</td>
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<td>I25.700-I25.799</td>
<td>Artherosclerosis of coronary artery bypass graft(s) and coronary artery of transplanted heart with angina pectoris</td>
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<td>Z13.6</td>
<td>Encounter for screening for cardiovascular disorders</td>
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