Medical Policy

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Title: Homocysteine Testing

Professional
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Current Effective Date: July 1, 2019

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic with risk of cardiovascular disease	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing, and therefore no supplementation	Relevant outcomes include: • Change in disease status • Morbid events
Individuals: • With cardiovascular disease	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing, and therefore no supplementation	Relevant outcomes include: • Change in disease status • Morbid events
Individuals: • Who are asymptomatic with risk of venous thromboembolism	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing, and therefore no supplementation	Relevant outcomes include: • Change in disease status • Morbid events

Populations	Interventions	Comparators	Outcomes
• Individuals: • Who have experienced venous thromboembolic events	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing, and therefore no supplementation	Relevant outcomes include: • Change in disease status • Morbid events

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 risk of CVD or thrombotic events has been examined.

Objective

The objective of this evidence review is to assess 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 the net health outcomes.

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 CVD (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.

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

POLICY

I. Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease

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

B. Measurement of plasma levels of homocysteine is considered **experimental / investigational** in the screening, evaluation, and management of patients with venous thromboembolism or risk of venous thromboembolism.

II. Other Homocysteine Testing

A. Homocysteine Testing may be considered **medically necessary** for non-cardiovascular diagnoses of:
1. homocystinuria
2. recurrent pregnancy loss
3. borderline vitamin B 12 deficiency

B. Homocysteine Testing is considered **experimental / investigational** for any other diagnoses.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 16, 2020.

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. Homocysteine levels are known to be associated with risk of CVD (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 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. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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 has even 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 CVD 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)

Study	Population	Outcomes	Major Findings (95% CI)
			• Among 501 subjects who took folic acid supplementation, 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=0.029) • 4th vs 1st quartile: adjusted HR=2.15 (1.01 to 4.63; p=0.049)
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 ^{3}85th percentile associated with high FRS: OR=2.1 (1.48 to 3.01) • Homocysteine levels at ^{3}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 patients at risk of CVD or in patients who have CVD is to inform management decisions such as whether to lower homocysteine levels.

The question addressed in this evidence review is: Does homocysteine testing of asymptomatic patients at risk of CVD or of patients who have CVD improve the net health outcome?

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

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

Interventions
The relevant intervention of interest is homocysteine testing.

Patients with or at risk of CVD may be assessed in the outpatient setting by a primary care medical provider or a specialist managing CVD.

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 is change 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.

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

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 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 randomized controlled trials (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.[8] 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.

Systematic Reviews

A Cochrane systematic review (2017[9]; originally published in 2009 and updated in 2013[10] and 2015[11]) 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 1,000 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.[12] 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.[13] Six trials (total 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<0.05). 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<0.05). 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.[14] Eight studies (total N=611 subjects) were included; folic acid doses ranged from 400 to 10000 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<0.001), 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.[15] This review had more lenient inclusion criteria because there was no limitation on study size or intervention duration. Nineteen trials (total 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.[16] 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.[17] This meta-analysis selected studies that included at least 1000 participants and had at least 1 year of follow-up. Eight trials (total 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-lower 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.[18] The trial included 2,929 subjects over age 65 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=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, 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.[19] 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 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).

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.[20] Patients were randomized to a regimen of folate, vitamin B_6, plus 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% versus 5.3%; RR=0.75; 95% CI, 0.59 to 0.97; p=0.03). 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=0.02).

The Norwegian Vitamin Trial (2006) enrolled 3749 patients with a recent MI who were randomized to combinations of folate and/or B vitamins.[21] 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=0.05) was observed for the primary composite outcome group.

Section Summary: Cardiovascular Disease

Numerous large placebo-controlled randomized trials evaluated the impact of folic acid and vitamin B supplementation on 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 patients at risk of VTE or of patients who have VTE events is to inform management decisions such as whether to lower homocysteine levels.

The question addressed in this evidence review is: Does the use of homocysteine testing of asymptomatic patients at risk of VTE or of patients who have had previous VTE events improve net health outcomes?

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

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

Interventions
The relevant intervention of interest is homocysteine testing.

Patients with or at risk of VTE may be assessed in the outpatient setting by a primary care medical provider or a specialist managing VTE.

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 change in disease status and morbid events associated with VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE).

The time frame from 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 VTE, 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 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.

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 deep vein thrombosis (DVT) and pulmonary embolism (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 hyperhomocysteinemic 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 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 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 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 the risk of symptomatic VTE. 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).

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.

Summary of Evidence
For individuals who are asymptomatic with the risk of CVD or individuals with CVD who receive homocysteine testing, the evidence includes observational studies and randomized controlled trials (RCTs) of homocysteine-lowering interventions. Relevant outcomes are change in disease status and morbid events such as cardiovascular (CV) events, including myocardial infarction, stroke, and CV death. Evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins improves CV outcomes. Numerous large RCTs and meta-analyses of these trials have consistently reported that homocysteine-lowering treatment is ineffective in reducing major CV events. A Cochrane systematic review found that homocysteine-lowering treatment reduced the risk of stroke. However, the investigators considered the results weak, and the clinical significance of this reduction is still unknown. Given a large amount of evidence from placebo-controlled randomized trials 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 the risk of venous thromboembolism (VTE) or individuals who have experienced VTE events who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. Relevant outcomes are change in disease status and morbid events such as VTE occurrence. Evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces the risk of VTE. Only a single RCT was designed to test for VTE as a primary outcome. The evidence is insufficient to determine that the technology results in an improvement in the net 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 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 and the American Stroke Association 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).

American College of Cardiology and American Heart Association
In 2019, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued a joint guideline on the primary prevention of CVD.[31,] 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.[32,] 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.[33,] 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.[34,] 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.[35,] 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 National Institute for Health and Care Excellence (2018; updated 2019) issued guidance on reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism.[36,] 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.[37,] Homocysteine levels were not mentioned in this recommendation.

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
Ongoing			
NCT00671346	Combined Analyses and Long-term Follow-up in the Two Norwegian Homocysteine Lowering B-Vitamin Trials NORVIT and WENBIT	6839	Jan 2021
NCT03122002	A Prospective Cohort Study of Predictors and Prognostic Factors on the Acute Ischemic Stroke	5000	Dec 2022

NCT: national clinical trial.

CODING

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

CPT/HCPCS

83090	Homocysteine

ICD-10 Diagnoses

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

Experimental / investigational for all diagnoses related to this policy language.

Other Homocysteine Testing

D51.0	Vitamin B12 deficiency anemia due to intrinsic factor deficiency
D51.1	Vitamin B12 deficiency anemia due to selective vitamin B12 malabsorption with proteinuria
D51.2	Transcobalamin II deficiency
D51.3	Other dietary vitamin B12 deficiency anemia
D51.8	Other vitamin B12 deficiency anemias
D51.9	Vitamin B12 deficiency anemia, unspecified
D53.1	Other megaloblastic anemias, not elsewhere classified
D68.8	Other specified coagulation defects
D68.9	Coagulation defect, unspecified
D81.818	Other biotin-dependent carboxylase deficiency
D81.819	Biotin-dependent carboxylase deficiency, unspecified
E53.8	Deficiency of other specified B group vitamins
E72.10	Disorders of sulfur-bearing amino-acid metabolism, unspecified
E72.11	Homocystinuria
E72.12	Methylenetetrahydrofolate reductase deficiency
E72.19	Other disorders of sulfur-bearing amino-acid metabolism
G60.3	Idiopathic progressive neuropathy

G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified
N96	Recurrent pregnancy loss
O03.2	Embolism following incomplete spontaneous abortion
O03.35	Other venous complications following incomplete spontaneous abortion
O03.39	Incomplete spontaneous abortion with other complications
O03.4	Incomplete spontaneous abortion without complication
O03.7	Embolism following complete or unspecified spontaneous abortion
O03.85	Other venous complications following complete or unspecified spontaneous abortion
O03.88	Urinary tract infection following complete or unspecified spontaneous abortion
O03.89	Complete or unspecified spontaneous abortion with other complications
O03.9	Complete or unspecified spontaneous abortion without complication
O26.21	Pregnancy care for patient with recurrent pregnancy loss, first trimester
O26.22	Pregnancy care for patient with recurrent pregnancy loss, second trimester
O26.23	Pregnancy care for patient with recurrent pregnancy loss, third trimester

REVISIONS	
08-17-2010	▪ The Homocysteine Testing and Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease medical policies were merged and entitled Homocysteine Testing.
	Description Section updated.
	In Policy Section: ▪ Added the following medically necessary non-cardiac indications for testing ▪ recurrent pregnancy loss ▪ venous thromboembolism ▪ Clarified that homocysteine testing for any diagnosis other than homocystinuria, recurrent pregnancy loss, borderline vitamin B 12 deficiency, or venous thromboembolism is considered E/I by adding, "Homocysteine Testing is considered **experimental / investigational** for any other diagnoses."
	Rationale Section updated.
	In Coding Section: ▪ Added Diagnosis codes: 281.0, 281.1, 281.3, 286.9, 356.4, 356.8, 356.9, 362.30, 415.11, 415.19, 444.0-444.1, 444.9, 451.0-451.9-, 452, 453.0, 453.1, 453.2, 453.3, 453.40-453.9, 454.0-454.9, 557.0, 629.81, 634.00-634.92, 646.30, 646.31, 646.33, V12.51
	References Section updated.
08-12-2011	Description section updated.
	Rationale section updated.
	In Coding section: ▪ Broke out the diagnosis coding range 453.40-453.9 to provide more detailed nomenclature ▪ Updated wording for diagnosis codes: 629.81, 646.30, 646.31, 646.33 ▪ No coding changes were made
	References updated.
06-29-2012	Description section updated
	Rationale section updated
	In Coding section: ▪ Diagnosis coding nomenclature updated
	References updated
03-31-2014	Description section updated
	Rationale section updated
	In Coding section: ▪ Removed ICD-9 Diagnoses codes: 444.01-444.1, 444.9, 454.0-454.9

	▪ ICD-10 Diagnoses codes added
	References updated
02-24-2016	Description section updated
	Rationale section updated
	References updated
10-01-2016	In Coding section: ▪ ICD-10 Codes Effective 10-01-2016: H34.8110, H34.8111, H34.8112, H34.8120, H34.8121, H34.8122, H34.8130, H34.8131, H34.8132, H34.8310, H34.8311, H34.8312, H34.8320,H34.8321, H34.8322,H34.8330, H34.8331, H34.8332, K55.011, K55.012, K55.019, K55.021, K55.022, K55.029, K55.031, K55.032, K55.039, K55.041, K55.042, K55.049 ▪ ICD-10 Codes Termed 09-30-2016: H34.9, K55.0
10-01-2017	In Coding section: ▪ Revise ICD-10 Code Nomenclature: I82.811, I82.812
07-01-2019	Description section updated
	In Policy Section ▪ In Item I added "and Venous Thromboembolic Disease" to read "Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease" ▪ In Item I added "B. Measurement of plasma levels of homocysteine is considered experimental / investigational in the screening, evaluation, and management of patients with venous thromboembolism or risk of venous thromboembolism." In Item II A removed "venous thromboembolism"
	Rationale section updated
	In Coding Section: Removed ICD-10 Codes: H34.8110, H34.8111, H34.8112, H34.8120, H34.8121, H34.8122, H34.8130, H34.8131, H34.8132, H34.8310, H34.8311, H34.8312, H34.8320, H34.8321, H34.8322, H34.8330, H34.8331, H34.8332, I26.09, I26.90, I26.99, I80.01, I80.02, I80.03, I80.11, I80.12, I80.13, I80.201, I80.202, I80.203, I80.211, I80.212, I80.213, I80.221, I80.222, I80.223, I80.231, I80.232, I80.233, I80.291, I80.292, I80.293, I80.8, I81, I82.0, I82.1, I82.210, I82.211, I82.220, I82.221, I82.290, I82.291 I82.3, I82.401, I82.402, I82.403, I82.411, I82.412, I82.413, I82.421, I82.422, I82.423, I82.431, I82.432, I82.433, I82.441, I82.442, I82.443, I82.491, I82.492, I82.493, I82.4Y1, I82.4Y2, I82.4Y3, I82.4Z1, I82.4Z2, I82.4Z3, I82.511, I82.512, I82.513, I82.521, I82.522, I82.523, I82.531, I82.532, I82.533, I82.541, I82.542, I82.543, I82.591, I82.592, I82.593, I82.5Y1, I82.5Y2, I82.5Y3, I82.5Z1, I82.5Z2, I82.5Z3, I82.601, I82.602, I82.603, I82.611, I82.612, I82.613, I82.621, I82.622, I82.623, I82.701, I82.702, I82.703, I82.711, I82.712, I82.713, I82.721, I82.722, I82.723, I82.811, I82.812, I82.813, I82.91, I82.A11, I82.A12, I82.A13, I82.A21, I82.A22, I82.A23, I82.B11, I82.B12, I82.B13, I82.B21, I82.B22, I82.B23, I82.C11, I82.C12, I82.C13, I82.C21, I82.C22, I82.C23, K55.011, K55.012, K55.019, K55.021, K55.022, K55.029, K55.031, K55.032, K55.039, K55.041, K55.042, K55.049, T81.72xA, T81.72xD, T81.72xS, Z86.718
	References updated
04-16-2021	Updated Description section
	Updated Rationale section
	Updated References section

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