

## Medical Policy



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

#### Professional

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#### DESCRIPTION

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

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

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

Determination of homocysteine 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.

#### POLICY

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

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

## **RATIONALE**

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

### 1. Homocysteine as a risk factor for CAD.

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

For patients with known CAD, prospective data are more consistent in supporting the utility of homocysteine as a risk factor for future events. For example, Nygard and colleagues prospectively studied the plasma homocysteine levels in 587 patients with angiographically confirmed coronary artery disease. (5) After a median follow-up of 4.6 years, the authors compared the initial homocysteine levels of the 64 patients (10.9%) who had died to those of the remaining 523 survivors. The authors reported a strong graded dose-response relation between plasma homocysteine and mortality. Stubbs and colleagues evaluated the relationship between plasma homocysteine levels and cardiac events in 440 patients with acute coronary syndromes admitted to the hospital. (6) Admission plasma homocysteine levels were not related to short-term outcomes at 28

days; however, in long-term follow-up, patients with homocysteine levels in the 2 highest quintiles had a 2.6-fold increase in the subsequent risk of a cardiac event.

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

A recent meta-analysis of 30 observational studies concluded that homocysteine was, in general, a modest independent risk factor for the occurrence of cardiovascular events and strokes. The association between homocysteine levels and CAD was much stronger in retrospective studies involving subjects diagnosed with vascular disease than in prospective studies of healthy individuals. (8) However, improved prediction of risk does not by itself result in better health outcomes. (9)

## 2 Homocysteine levels as a modifiable risk factor.

Several limitations are involved in evaluating whether or not reducing homocysteine levels leads to reduced cardiovascular risk. Currently, no target levels exist for optimal homocysteine levels. Also, adherence to a diet meeting the recommended daily allowance (RDA) for folate intake, regardless of homocysteine and/or folate levels, could result in decreased levels of homocysteine. In addition, in 1996, the U.S. Food and Drug Administration (FDA) required that all enriched grain products be fortified with folic acid to reduce the risk of neural-tube defects in newborns. This fortification has been associated with a decrease in homocysteine concentration.(10) Trials of homocysteine-lowering therapy, therefore, should evaluate the utility of treatments that lower homocysteine levels beyond those achieved by these general public health measures.

Several recent investigations have attempted to establish a role for homocysteine-lowering vitamin therapy for the secondary prevention of atherosclerosis. In these patients, homocysteine lowering has been associated with favorable alterations in some vascular disease surrogates, such as ultrasound-measured endothelial function and exercise EKG. (11, 12) A recent prospective, double-blind, randomized trial showed a reduction in restenosis after percutaneous coronary intervention in patients receiving post-procedure vitamin supplementation. (13) Following coronary angioplasty, 205 patients were randomly assigned to receive a combination of folic acid, vitamin B<sub>12</sub>, and pyridoxine versus placebo for 6 months. Patients receiving the "folate treatment" had a significant reduction in angiographic restenosis rates (19.6% vs. 37.6%), which correlated with a reduction in serum homocysteine values. The need for target vessel revascularization was also significantly lower at 6 and 12 months in the treated group (14).

However, these data are not sufficient to establish that measurement of homocysteine improves outcomes. This study treated all post-angioplasty patients with folate, and did not use homocysteine levels to select patients for treatment. There are also limitations on the generalizability of these results to North American patients. The study was performed at a single center in Switzerland. The ability to lower homocysteine levels and to achieve potential benefits is likely to be weaker for patients in the United States, given the widespread supplementation of grain products with folate. In addition, the adjunctive use of stents and glycoprotein IIb/IIIa inhibitors in this study was substantially less than that used in North America. This is of particular importance because the difference in restenosis rates between the 2 groups did not achieve statistical significance in stented vessels. Furthermore, it is unclear whether vitamin supplementation would add additional benefit in arteries treated with modified (e.g., sirolimus-eluting) stent types. (15)

Given the limitations of the present data, the American Heart Association does not recommend population-wide screening for homocysteine levels. (16) This statement suggests that measurement of plasma homocysteine may have some role in patients with a personal or family history consistent with premature cardiovascular disease, with the suggestion that those with levels above 10.0  $\mu\text{mol/L}$  be advised to increase their intake of folic acid. However the outcomes of this treatment strategy have not been addressed in controlled trials.

Several ongoing trials, collectively enrolling over 50,000 subjects, are investigating the effect of homocysteine-lowering therapy on cardiovascular morbidity and mortality. Trials in North America include the Heart Outcomes Prevention Evaluation (HOPE-2) Study, the Vitamins in Stroke Prevention (VISP) Trial, and the Women's Antioxidant and Cardiovascular Disease (WACS). These investigations will provide more definitive data regarding the effect of homocysteine-lowering treatments on CAD events in North American patients. However, the statistical power of these studies to detect a clinical benefit from homocysteine lowering may be impaired by the population-wide effects of folate-enriched grains. (17)

However, improved prediction of risk does not by itself result in better health outcomes. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. This process involves guidelines that incorporate emerging risk factors into existing risk prediction models that are demonstrated to more accurately classify patients into risk categories and that are accompanied by treatment guidelines that better target interventions toward patients who will benefit the most.

### **2004-2005 Update**

A literature search for the period of 2003 through June 2005 did not identify any published studies that would address the above limitations. Studies continue to explore homocysteine as a cardiac risk factor. (18, 19) Studies of lipid-lowering therapy have also included measurements of homocysteine as an intermediate outcome, but there are still inadequate data to show how this laboratory test may be used to improve patient

management. (20, 21) Two randomized studies have explored the role of folic acid administration as a technique to reduce homocysteine levels in patients with CAD and stroke. (22, 23) However, treatment was not based on serum levels of homocysteine; all patients randomized to the treatment group received folic acid. In addition, both studies reported that folic acid supplementation was not associated with improved outcomes.

### **2006 Update**

A literature search for the period of July 2005 through June 2006 did not identify any published studies that would alter the policy statements above. Additional studies have been published that evaluated treatments to reduce homocysteine levels on vascular events. Bonaa and colleagues found that treatment to lower homocysteine (folate and B vitamins) did lower homocysteine levels but did not lower the risk of recurrent cardiovascular disease in patients who had experienced a recent myocardial infarction; they also noted a trend toward increased risk in some patients. (24) Similarly, investigators for the HOPE 2 trial (Heart Outcomes Prevention Evaluation) found that supplements of folic acid and vitamins B<sub>6</sub> and B<sub>12</sub> did reduce homocysteine levels but did not reduce the risk of major cardiovascular events in patients with vascular disease. (25) Finally, McMahon and colleagues reported that lowering homocysteine levels did not improve cognitive performance during a 2-year study. (26)

### **2008 Update**

Epidemiological studies and small controlled trials using surrogate outcome measures (flow-mediated dilation, intimal wall thickness, etc.) were published, which add to the considerable body of literature on this topic, but not sufficiently to change the policy statement. Two meta-analyses of trials of folic acid supplementation for secondary prevention of cardiovascular diseases were published. (27, 28) The analyses included many of the same randomized, controlled trials and showed nearly the same pooled relative risk, but came to alternative conclusions about their results. The study by Bazzano and colleagues (27) included nearly 17,000 subjects from 12 studies and concluded that folic acid supplementation does not reduce the risk of cardiovascular disease (relative risk [RR] 0.95; 95% CI: 0.88–1.03) or all-cause mortality (RR 0.96; 95%CI: 0.88– 1.04) and that clinicians should focus their energies on proven cardiovascular risk reduction strategies such as smoking cessation, control of hypertension and lipid-lowering therapies. An alternative conclusion was reached by Wald and colleagues (28), who found similar relative risk (outcome of ischemic heart disease, RR 0.98; 95% CI: 0.78–1.05) in 7 studies of over 15,000 subjects. However, they concluded that the weight of observational and genetic studies combined with the possibility that the trials were underpowered to detect small changes in relative risk and that they might not have been of sufficient duration to show a benefit, prevented concluding a null effect. At this time, the evidence suggests that treatment of hyperhomocysteinemia with folic acid is ineffective, and the utility of screening for hyperhomocysteinemia is, therefore, questionable. Further trials, including approximately 50,000 subjects are forthcoming. (29)

## **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

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