Medical Coverage Policy | Homocysteine Testing in the Screening and Diagnosis and Management of Cardiovascular Disease

EFFECTIVE DATE: 06|01|2019
POLICY LAST UPDATED: 01|18|2023

OVERVIEW
Homocysteine is an amino acid found in the blood; levels are inversely correlated with folate levels. Homocysteine has been evaluated as a potential marker of cardiovascular disease (CVD) in the general population and as a potential risk marker among people with CVD. The association between homocysteine-lowering interventions and risk of CVD has also been examined.

MEDICAL CRITERIA
Not applicable

PRIOR AUTHORIZATION
Not applicable

POLICY STATEMENT
Medicare Advantage Plans
Measurement of plasma levels of homocysteine are not covered in the screening, evaluation and management of patients with the following indications due to the large amount of evidence that homocysteine-lowering interventions do not improve health outcomes

- individuals for cardiovascular disease
- individuals with venous thromboembolism or risk of venous thromboembolism.

Commercial Products
Measurement of plasma levels of homocysteine is considered not medically necessary in the screening, evaluation and management of patients with the following indications due to the large amount of evidence that homocysteine-lowering interventions do not improve health outcomes

- individuals for cardiovascular disease
- individuals with venous thromboembolism or risk of venous thromboembolism.

COVERAGE
Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND
Homocysteine is a sulfur-containing amino acid that is rapidly oxidized in plasma into homocysteine and cysteine-homocysteine disulfide. Measurement of total plasma homocysteine is the sum of homocysteine and its oxidized forms.

Plasma levels of homocysteine have been actively researched as a risk factor for cardiovascular disease (CVD), initially based on the observation that patients with hereditary homocystinuria, an inborn error of metabolism associated with high plasma levels of homocysteine, had a markedly increased risk of CVD. Subsequently, prospective epidemiologic studies were conducted to determine if an elevated plasma level of homocysteine was an independent risk factor for CVD and could be used to improve current risk prediction models. Several case-control studies have also suggested that elevated homocysteine is a risk factor for venous thromboembolism (VTE; pulmonary embolism, deep vein thrombosis).

Interest in homocysteine as a potentially modifiable risk factor has been stimulated by the epidemiologic finding that levels of homocysteine inversely correlate with levels of folate. This finding has raised the possibility that treatment with folic acid might lower homocysteine levels and, in turn, reduce the risk of CVD and thrombotic events. Therefore, homocysteine has a potential utility both as a risk predictor and as a target of treatment.

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

For individuals who are asymptomatic with the risk of CVD or individuals with CVD who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. Relevant outcomes are changes in disease status and morbid events such as CV events, including MI, 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 insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with the risk of 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 outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s) is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

83090 Assay of Homocysteine

RELATED POLICIES

Not applicable

PUBLISHED

Provider Update, March 2023
Provider Update, April 2022
Provider Update, March 2021
Provider Update, April 2020
Provider Update, August 2018

REFERENCES:

1. Veeranna V, Zalawadiya SK, Niraj A, et al. Homocysteine and reclassification of cardiovascular disease risk. J Am Coll Cardiol.Aug 30 2011; 58(10): 1025-33. PMID 21867837
2. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA. Oct2002; 288(16): 2015-22. PMID 12387654
3. Shoamanesh A, Preis SR, Beiser AS, et al. Circulating biomarkers and incident ischemic stroke in the Framingham OffspringStudy. Neurology. Sep 20 2016; 87(12): 1206-11. PMID 27558379
4. Han L, Wu Q, Wang C, et al. Homocysteine, Ischemic Stroke, and Coronary Heart Disease in Hypertensive Patients: APopulation-Based, Prospective Cohort Study. Stroke. Jul 2015; 46(7): 1777-86. PMID 26038522
5. Shi Z, Guan Y, Huo YR, et al. Elevated Total Homocysteine Levels in Acute Ischemic Stroke Are Associated With Long-TermMortality. Stroke. Sep 2015; 46(9): 2419-25. PMID 26199315
6. Wang C, Han L, Wu Q, et al. Association between homocysteine and incidence of ischemic stroke in subjects with essentialhypertension: a matched case-control study. Clin Exp Hypertens. 2015; 37(7): 557-62. PMID 25992490
7. Park CS, Ihm SH, Yoo KD, et al. Relation between C-reactive protein, homocysteine levels, fibrinogen, and lipoprotein levelsand leukocyte and platelet counts, and 10-year risk for cardiovascular disease among healthy adults in the USA. Am J Cardiol.May 01 2010; 105(9): 1284-8. PMID 20403480
8. Martí-Carvajal AJ, Solà I, Lathyris D, et al. Homocysteine-lowering interventions for preventing cardiovascular events.Cochrane Database Syst Rev. Aug 17 2017; 8(8): CD006612. PMID 28816346
9. Martí-Carvajal AJ, Solà I, Lathyris D, et al. Homocysteine-lowering interventions for preventing cardiovascular events.Cochrane Database Syst Rev. Jan 31 2013; (1): CD006612. PMID 23440809
10. Martí-Carvajal AJ, Solà I, Lathyris D. Homocysteine-lowering interventions for preventing cardiovascular events. CochraneDatabase Syst Rev. Jan 15 2015; 1: CD006612. PMID 25590290
11. Park JH, Saposnik G, Ovbiagele B, et al. Effect of B-vitamins on stroke risk among individuals with vascular disease who arenot on antiplatelets: A meta-analysis. Int J Stroke. Feb 2016; 11(2): 206-11. PMID 26783312
12. Yi X, Zhou Y, Jiang D, et al. Efficacy of folic acid supplementation on endothelial function and plasma homocysteineconcentration in coronary artery disease: A meta-analysis of randomized controlled trials. Exp Ther Med. May 2014; 7(5): 1100-1110. PMID 24940394
13. Liu Y, Tian T, Zhang H, et al. The effect of homocysteine-lowering therapy with folic acid on flow-mediated vasodilation inpatients with coronary artery disease: a meta-analysis of randomized controlled trials. Atherosclerosis. Jul 2014; 235(1): 31-5.PMID 24814647
14. Huang T, Chen Y, Yang B, et al. Meta-analysis of B vitamin supplementation on plasma homocysteine, cardiovascular and all-cause mortality. Clin Nutr. Aug 2012; 31(4): 448-54. PMID 22652362
15. Zhou YH, Tang JY, Wu MJ, et al. Effect of folic acid supplementation on cardiovascular outcomes: a systematic review andmeta-analysis. PLoS One. 2011; 6(9): e25142. PMID 21980387
16. Clarke R, Halsey J, Bennett D, et al. Homocysteine and vascular disease: review of published results of the homocysteine-lowering trials. J Inherit Metab Dis. Feb 2011; 34(1): 83-91. PMID 21069462
17. van Dijk SC, Enneman AW, Swart KM, et al. Effects of 2-year vitamin B12 and folic acid supplementation inhyperhomocysteinemic elderly on arterial stiffness and cardiovascular outcomes within the B-PROOF trial. J Hypertens. Sep2015; 33(9): 1897-906; discussion 1906. PMID 26147383
18. Armitage JM, Bowman L, Clarke RJ, et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo onmortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA. Jun 23 2010; 303(24): 2486-94.PMID 20571015
19. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med. Apr13 2006; 354(15): 1567-77. PMID 16531613
20. Bønaa KH, Njølstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. NEngl J Med. Apr 13 2006; 354(15): 1578-88. PMID 16531614
21. Jacques PF, Selhub J, Bostom AG, et al. The effect of folic acid fortification on plasma folate and total homocysteineconcentrations. N Engl J Med. May 13 1999; 340(19): 1449-54. PMID 10320382
22. Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of publishedepidemiological studies. J Thromb Haemost. Feb 2005; 3(2): 292-9. PMID 15670035

23. Ray JG. Meta-analysis of hyperhomocysteinemia as a risk factor for venous thromboembolic disease. Arch Intern Med. Oct 261998; 158(19): 2101-6. PMID 9801176
24. den Heijer M, Rosendaal FR, Blom HJ, et al. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. ThrombHaemost. Dec 1998; 80(6): 874-7. PMID 9869152
25. Naess IA, Christiansen SC, Romundstad PR, et al. Prospective study of homocysteine and MTHFR 677TT genotype and riskfor venous thrombosis in a general population--results from the HUNT 2 study. Br J Haematol. May 2008; 141(4): 529-35. PMID18318759