Medical Policy

BlueCross BlueShield of Kansas
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Title: Homocysteine Testing

Professional
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DESCRIPTION

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.

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 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 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 cardiovascular disease. 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, subclassification of high-density lipoproteins, evaluation of lipoprotein (a), high-sensitivity C-reactive protein, and genotyping of apolipoprotein E.

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. These include the liquid-stable two-part homocysteine reagent test by Catch Incorporated (Maple Valley, WA) in 2006. Catch Inc. was purchased by Axis-Shield (Scotland) in 2010 and the Catch branded products were phased out in 2011. The test is indicated for the in vitro quantitative determination of total homocysteine in serum and plasma to assist in diagnosing and treating patients with suspicion of homocystinuria and hyperhomocysteinemia.

POLICY

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

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

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
   4. venous thromboembolism

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

RATIONALE

This policy was updated with searches of the MEDLINE database. The most recent literature search was performed for the period February 2012 through March 6, 2013. 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 in order for a cardiovascular risk factor to demonstrate clinical utility. A 2002 TEC Assessment (1) summarized three 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 to established risk factors.
- Determination of how the novel risk factor will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcomes.

Is measurement of homocysteine standardized?
There are FDA-cleared commercially available kits for measuring homocysteine.

Is homocysteine an independent risk factor for cardiovascular disease?
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 or stroke. (2) 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 were 0.83 (95% confidence interval [CI]: 0.77 to 0.89) in prospective studies, 0.67 (95% CI: 0.62-0.71) in retrospective studies using population controls, and 0.73 (95% CI: 0.64-0.83) in retrospectives studies with other controls. The adjusted OR of stroke associated with a 25% lower homocysteine level was 0.77 (95% CI: 0.66-0.90) in prospective studies, 0.86 (95% CI: 0.73-1.01) in retrospective studies with population controls, and 0.46 (95% CI: 0.30-0.70) in retrospective studies with other controls. The authors noted that the risk of ischemic heart disease and stroke was significantly weaker in the prospective studies than the retrospectives studies, which may reflect biases in retrospective studies.

Among the prospective studies was one by Folsom and colleagues that identified patients who developed coronary heart disease among an initial cohort of 15,792 patients participating in the Atherosclerosis Risk in Communities (ARIC) trial. (3) 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 coronary artery disease (CAD), this association was not significant after adjusting for other cardiac risk factors in multivariate analysis. Another prospective study was published by Evans and colleagues. (4) 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 coronary heart disease (CHD). Moreover, 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 who were drawn from the original study of 21,520 men. (5)

In 2010, Park and colleagues published an analysis of data from a large nationally representative survey of U.S. residents. (6) The analysis was restricted to the 6,371 individuals aged 40-79 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 cardiovascular disease (CVD), using the Framingham risk score; low-risk, less than 10% (n=2,527), intermediate-risk, 10-20% (n=3,336), and high-risk, greater than 20% (n=508). Information on homocysteine level was available for 3,860 (61%) patients. There was a statistically significant association between elevated homocysteine levels (defined as at least the 85% 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, and conclusions cannot be drawn about the value of knowing homocysteine levels.

For patients with known cardiovascular disease, prospective data are more consistent in supporting the utility of homocysteine as a risk factor for future events. In 1997, for example, Nygard and colleagues reported on a prospective study of the plasma homocysteine levels in 587 patients with angiographically confirmed coronary artery disease. (7) 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 relationship between plasma homocysteine and mortality. In addition, Knekt and colleagues reported the outcomes at 13 years' follow-up of 3,471 middle-aged Finnish men, 884 of whom had known cardiovascular disease at baseline. (8) 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 cardiovascular disease 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.

In 2011, Veeranna and colleagues published a post-hoc analysis of national survey databases to evaluate whether adding homocysteine to the Framingham risk score model improves risk classification. (9) The data were taken from the nationally representative surveys Multi-Ethnic Study of Atherosclerosis (MESA), which included individuals 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 non-institutionalized individuals. Homocysteine level was associated with CVD risk in both databases. In a receiver-operating curve (ROC) 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, $p<0001$. Adding homocysteine to the Framingham model resulted in reclassification of 832 (12.9%) individuals in the MESA cohort and 1,243 (18%) in the NHANES III cohort. This study does not address whether testing for homocysteine would improve health outcomes. This would involve evaluating the impact of homocysteine-lowering interventions on risk of cardiovascular disease, which is discussed in the next section of the policy.

Conclusions: A meta-analysis of observational studies found a statistically significant moderate association between homocysteine levels and risk of cardiovascular disease. Studies have also found a significant correlation between homocysteine levels in individuals with known cardiovascular disease 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; the clinical significance of adding homocysteine to the Framingham model was not addressed.

Will identification of homocysteine level lead to changes in patient management, and will these changes in management lead to improved 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 homocysteine concentration. (10) 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. Most recently, in 2013, a Cochrane systematic review on the effectiveness of homocysteine-lowering interventions for preventing cardiovascular events was updated. (11) The review included trials that recruited adults with established CVD and had at least 1 year of follow-up and

excluded trials with end-stage renal disease patients. Twelve trials with a total of 47,429 participants met eligibility criteria. Nine of the studies included more than 1,000 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 non-fatal 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 non-fatal 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 and colleagues conducted a systematic review of double-blind placebo-controlled RCTs evaluating the impact of folic acid supplementation on cardiovascular outcomes. (12) 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 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 to 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), myocardial infarction (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 and colleagues published a meta-analysis of placebo-controlled homocysteine-lowering RCTs. (13) This meta-analysis was limited to studies that included at least 1,000 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 coronary heart disease (CHD) events compared to 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 fourth meta-analysis, published in 2012 by Huang and colleagues, included RCTs evaluating B vitamin supplementation in patients with pre-existing vascular disease. (14) 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 discussed above, 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, myocardial infarction 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.

Representative RCTs are described below:

The HOPE-2 trial included 5,522 patients with pre-existing 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. (15) There were no significant differences in the composite outcome of cardiovascular death, MI, or stroke (relative risk [RR]: 0.95; 95% CI:

0.84–1.07). However, there was a significant decrease in the risk of stroke for patients in the treatment group (RR: 0.75; 95% CI: 0.59-0.97, 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: 1.04-1.49, p=0.02).

The NORVIT enrolled 3,749 patients with a recent MI and randomized patients to combinations of folate and/or B vitamins. (16) 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: 1.00–1.50, 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. (17) 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. Prior to 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 3-4 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 1,537 (25.5%) in the vitamin group and 1,493 (24.8%) in the placebo group (RR: 1.04; 95% CI: 0.97-1.12). 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).

Conclusions: Numerous large placebo-controlled RCTs have been published that evaluate the impact of folic acid/ vitamin B supplementation on risk of cardiovascular events. 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.

Summary

Observational evidence generally supports the association of homocysteine levels with risk of cardiovascular disease, especially in patients with pre-existing vascular disease. However, evidence from randomized controlled trials does not support the hypothesis that lowering homocysteine levels by treatment with folate and/or B vitamins improves cardiovascular outcomes. Numerous large, randomized controlled trials and meta-analyses of these trials are consistent in reporting that homocysteine-lowering treatment is ineffective in reducing major cardiovascular events. Due to the large amount of evidence from placebo-controlled RCTs that homocysteine-lowering interventions do not improve health outcomes, routine testing for homocysteine and intervention for patients with hyperhomocysteinemia is considered investigational.

Practice Guidelines and Position Statements
In 2009, the U.S. Preventive Services Task Force (USPSTF) issued a recommendation statement that the evidence is insufficient (one 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. (18)

A 2010 statement (updated January 2012) issued by the American Heart Association (AHA) states that the organization does not consider high homocysteine levels in the blood to be a major risk factor for cardiovascular disease. (19) It further states that a causal link between homocysteine levels and atherosclerosis has not been established.

A 2010 guideline from the American College of Cardiology Foundation and the American Heart Association on assessment of cardiovascular risk in asymptomatic adults did not address measurement of homocysteine levels. (20)

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-9 Diagnoses
Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease
Experimental / investigational for all diagnoses related to this policy.

Other Homocysteine Testing

266.2	Other B-complex deficiencies
270.4	Disturbance of sulphur-bearing amino-acid metabolism
281.0	Pernicious anemia
281.1	Other vitamin B12 deficiency anemia
281.3	Other specified megaloblastic anemias not elsewhere classified
286.9	Other and unspecified coagulation defects
356.4	Idiopathic progressive polyneuropathy
356.8	Other specified idiopathic peripheral neuropathy
356.9	Unspecified hereditary and idiopathic peripheral neuropathy
362.30	Unspecified retinal vascular occlusion
415.11	Iatrogenic pulmonary embolism and infarction
415.19	Other pulmonary embolism and infarction
451.0-451.9	Phlebitis and thrombophlebitis (code range)
452	Portal vein thrombosis
453.0	Budd-Chiari syndrome

453.1	Thrombophlebitis migrans
453.2	Other venous embolism and thrombosis; of inferior vena cava
453.3	Other venous embolism and thrombosis; of renal vein
453.40-453.42	Acute venous embolism and thrombosis of deep vessels of lower extremity (code range)
453.50-453.52	Chronic venous embolism and thrombosis of deep vessels of lower extremity (code range)
453.6	Venous embolism and thrombosis of superficial vessels of lower extremity
453.71-453.79	Chronic venous embolism and thrombosis of other specified vessels (code range)
453.81-453.89	Acute venous embolism and thrombosis of other specified veins (code range)
453.9	Other venous embolism and thrombosis; of unspecified site
557.0	Acute vascular insufficiency of intestine
629.81	Recurrent pregnancy loss without current pregnancy
634.00-634.92	Spontaneous abortion (code range)
646.30	Recurrent pregnancy loss, unspecified as to episode of care
646.31	Recurrent pregnancy loss, with or without mention of antepartum condition
646.33	Recurrent pregnancy loss, antepartum condition or complication
V12.51	Venous thrombosis and embolism

ICD-10 Diagnoses (Effective October 1, 2014)

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

Experimental / investigational for all diagnoses related to this policy.

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
H34.9	Unspecified retinal vascular occlusion
I26.09	Other pulmonary embolism with acute cor pulmonale
I26.90	Septic pulmonary embolism without acute cor pulmonale

I26.99	Other pulmonary embolism without acute cor pulmonale
I80.01	Phlebitis and thrombophlebitis of superficial vessels of right lower extremity
I80.02	Phlebitis and thrombophlebitis of superficial vessels of left lower extremity
I80.03	Phlebitis and thrombophlebitis of superficial vessels of lower extremities, bilateral
I80.11	Phlebitis and thrombophlebitis of right femoral vein
I80.12	Phlebitis and thrombophlebitis of left femoral vein
I80.13	Phlebitis and thrombophlebitis of femoral vein, bilateral
I80.201	Phlebitis and thrombophlebitis of unspecified deep vessels of right lower extremity
I80.202	Phlebitis and thrombophlebitis of unspecified deep vessels of left lower extremity
I80.203	Phlebitis and thrombophlebitis of unspecified deep vessels of lower extremities, bilateral
I80.211	Phlebitis and thrombophlebitis of right iliac vein
I80.212	Phlebitis and thrombophlebitis of left iliac vein
I80.213	Phlebitis and thrombophlebitis of iliac vein, bilateral
I80.221	Phlebitis and thrombophlebitis of right popliteal vein
I80.222	Phlebitis and thrombophlebitis of left popliteal vein
I80.223	Phlebitis and thrombophlebitis of popliteal vein, bilateral
I80.231	Phlebitis and thrombophlebitis of right tibial vein
I80.232	Phlebitis and thrombophlebitis of left tibial vein
I80.233	Phlebitis and thrombophlebitis of tibial vein, bilateral
I80.291	Phlebitis and thrombophlebitis of other deep vessels of right lower extremity
I80.292	Phlebitis and thrombophlebitis of other deep vessels of left lower extremity
I80.293	Phlebitis and thrombophlebitis of other deep vessels of lower extremity, bilateral
I80.8	Phlebitis and thrombophlebitis of other sites
I81	Portal vein thrombosis
I82.0	Budd-Chiari syndrome
I82.1	Thrombophlebitis migrans
I82.210	Acute embolism and thrombosis of superior vena cava
I82.211	Chronic embolism and thrombosis of superior vena cava
I82.220	Acute embolism and thrombosis of inferior vena cava
I82.221	Chronic embolism and thrombosis of inferior vena cava
I82.290	Acute embolism and thrombosis of other thoracic veins
I82.291	Chronic embolism and thrombosis of other thoracic veins
I82.3	Embolism and thrombosis of renal vein
I82.401	Acute embolism and thrombosis of unspecified deep veins of right lower extremity
I82.402	Acute embolism and thrombosis of unspecified deep veins of left lower extremity
I82.403	Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral
I82.411	Acute embolism and thrombosis of right femoral vein
I82.412	Acute embolism and thrombosis of left femoral vein
I82.413	Acute embolism and thrombosis of femoral vein, bilateral
I82.421	Acute embolism and thrombosis of right iliac vein
I82.422	Acute embolism and thrombosis of left iliac vein
I82.423	Acute embolism and thrombosis of iliac vein, bilateral
I82.431	Acute embolism and thrombosis of right popliteal vein
I82.432	Acute embolism and thrombosis of left popliteal vein
I82.433	Acute embolism and thrombosis of popliteal vein, bilateral
I82.441	Acute embolism and thrombosis of right tibial vein
I82.442	Acute embolism and thrombosis of left tibial vein

I82.443 Acute embolism and thrombosis of tibial vein, bilateral
I82.491 Acute embolism and thrombosis of other specified deep vein of right lower extremity
I82.492 Acute embolism and thrombosis of other specified deep vein of left lower extremity
I82.493 Acute embolism and thrombosis of other specified deep vein of lower extremity, bilateral
I82.4Y1 Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity
I82.4Y2 Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity
I82.4Y3 Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral
I82.4Z1 Acute embolism and thrombosis of unspecified deep veins of right distal lower extremity
I82.4Z2 Acute embolism and thrombosis of unspecified deep veins of left distal lower extremity
I82.4Z3 Acute embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral
I82.511 Chronic embolism and thrombosis of right femoral vein
I82.512 Chronic embolism and thrombosis of left femoral vein
I82.513 Chronic embolism and thrombosis of femoral vein, bilateral
I82.521 Chronic embolism and thrombosis of right iliac vein
I82.522 Chronic embolism and thrombosis of left iliac vein
I82.523 Chronic embolism and thrombosis of iliac vein, bilateral
I82.531 Chronic embolism and thrombosis of right popliteal vein
I82.532 Chronic embolism and thrombosis of left popliteal vein
I82.533 Chronic embolism and thrombosis of popliteal vein, bilateral
I82.541 Chronic embolism and thrombosis of right tibial vein
I82.542 Chronic embolism and thrombosis of left tibial vein
I82.543 Chronic embolism and thrombosis of tibial vein, bilateral
I82.591 Chronic embolism and thrombosis of other specified deep vein of right lower extremity
I82.592 Chronic embolism and thrombosis of other specified deep vein of left lower extremity
I82.593 Chronic embolism and thrombosis of other specified deep vein of lower extremity, bilateral
I82.5Y1 Chronic embolism and thrombosis of unspecified deep veins of right proximal lower extremity
I82.5Y2 Chronic embolism and thrombosis of unspecified deep veins of left proximal lower extremity
I82.5Y3 Chronic embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral
I82.5Z1 Chronic embolism and thrombosis of unspecified deep veins of right distal lower extremity
I82.5Z2 Chronic embolism and thrombosis of unspecified deep veins of left distal lower extremity
I82.5Z3 Chronic embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral
I82.601 Acute embolism and thrombosis of unspecified veins of right upper extremity
I82.602 Acute embolism and thrombosis of unspecified veins of left upper extremity

I82.603	Acute embolism and thrombosis of unspecified veins of upper extremity, bilateral
I82.611	Acute embolism and thrombosis of superficial veins of right upper extremity
I82.612	Acute embolism and thrombosis of superficial veins of left upper extremity
I82.613	Acute embolism and thrombosis of superficial veins of upper extremity, bilateral
I82.621	Acute embolism and thrombosis of deep veins of right upper extremity
I82.622	Acute embolism and thrombosis of deep veins of left upper extremity
I82.623	Acute embolism and thrombosis of deep veins of upper extremity, bilateral
I82.701	Chronic embolism and thrombosis of unspecified veins of right upper extremity
I82.702	Chronic embolism and thrombosis of unspecified veins of left upper extremity
I82.703	Chronic embolism and thrombosis of unspecified veins of upper extremity, bilateral
I82.711	Chronic embolism and thrombosis of superficial veins of right upper extremity
I82.712	Chronic embolism and thrombosis of superficial veins of left upper extremity
I82.713	Chronic embolism and thrombosis of superficial veins of upper extremity, bilateral
I82.721	Chronic embolism and thrombosis of deep veins of right upper extremity
I82.722	Chronic embolism and thrombosis of deep veins of left upper extremity
I82.723	Chronic embolism and thrombosis of deep veins of upper extremity, bilateral
I82.811	Embolism and thrombosis of superficial veins of right lower extremities
I82.812	Embolism and thrombosis of superficial veins of left lower extremities
I82.813	Embolism and thrombosis of superficial veins of lower extremities, bilateral
I82.91	Chronic embolism and thrombosis of unspecified vein
I82.A11	Acute embolism and thrombosis of right axillary vein
I82.A12	Acute embolism and thrombosis of left axillary vein
I82.A13	Acute embolism and thrombosis of axillary vein, bilateral
I82.A21	Chronic embolism and thrombosis of right axillary vein
I82.A22	Chronic embolism and thrombosis of left axillary vein
I82.A23	Chronic embolism and thrombosis of axillary vein, bilateral
I82.B11	Acute embolism and thrombosis of right subclavian vein
I82.B12	Acute embolism and thrombosis of left subclavian vein
I82.B13	Acute embolism and thrombosis of subclavian vein, bilateral
I82.B21	Chronic embolism and thrombosis of right subclavian vein
I82.B22	Chronic embolism and thrombosis of left subclavian vein
I82.B23	Chronic embolism and thrombosis of subclavian vein, bilateral
I82.C11	Acute embolism and thrombosis of right internal jugular vein
I82.C12	Acute embolism and thrombosis of left internal jugular vein
I82.C13	Acute embolism and thrombosis of internal jugular vein, bilateral
I82.C21	Chronic embolism and thrombosis of right internal jugular vein
I82.C22	Chronic embolism and thrombosis of left internal jugular vein
I82.C23	Chronic embolism and thrombosis of internal jugular vein, bilateral
K55.0	Acute vascular disorders of intestine
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
T81.72xA	Complication of vein following a procedure, not elsewhere classified, initial encounter
T81.72xD	Complication of vein following a procedure, not elsewhere classified, subsequent encounter
T81.72xS	Complication of vein following a procedure, not elsewhere classified, sequela
Z86.718	Personal history of other venous thrombosis and embolism

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

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