Hyperhomocysteinemia and Atherosclerotic Vascular Disease
Pathophysiology, Screening, and Treatment

James H. Stein, MD; Patrick E. McBride, MD, MPH

Hyperhomocysteinemia has recently been identified as an important risk factor for atherosclerotic vascular disease. This article reviews homocysteine metabolism, causes of hyperhomocysteinemia, the pathophysiological findings of this disorder, and epidemiological studies of homocysteine and vascular disease. Screening for hyperhomocysteinemia should be considered for patients at high risk for vascular disease or abnormalities of homocysteine metabolism. For primary prevention of vascular disease, treatment of patients with homocysteine levels of 14 µmol/L or higher should be considered. For secondary prevention, treatment of patients with homocysteine levels of 11 µmol/L or higher should be considered. Treatment is most conveniently administered as a folic acid supplement (400-1000 µg) and a high-potency multivitamin that contains at least 400 µg of folate. Higher doses of folic acid and cyanocobalamin supplements may be required in some patients. Until prospective clinical trial data become available, these conservative recommendations provide a safe, effective, and evidence-based approach to the diagnosis, evaluation, and management of patients with hyperhomocysteinemia.

The observation that up to 19% of patients in large clinical trials of low-density lipoprotein cholesterol–lowering therapy experienced adverse cardiovascular events, despite this powerful intervention, has intensified the search for new, nonlipid risk factors for atherosclerotic vascular disease (ASVD).1-4 Hyperhomocysteinemia, a metabolic abnormality that can be detected in up to 30% of patients with coronary artery disease (CAD) and 42% of patients with cerebrovascular disease, recently has been identified as an important risk factor for ASVD.4-6 The purpose of this article is to provide an evidence-based approach to the diagnosis and management of patients with hyperhomocysteinemia. In this context, homocysteine metabolism, the causes of hyperhomocysteinemia, and the pathophysiologica findings of this disorder are reviewed, as are the epidemiological studies that have implicated hyperhomocysteinemia as a predictor of increased risk of ASVD. On the basis of these discussions, practical recommendations for the screening and treatment of patients with this disorder are provided.

HOMOCYSTEINE METABOLISM

Homocysteine is an amino acid intermediate in the metabolism of methionine, an essential amino acid found in both animal and plant proteins (Figure 1). The recommended daily allowance of methionine is 0.9 g; however, the average American diet contains approximately 2 g/d of methionine, the excess of which is converted via enzymatic transmethylation to homocysteine.6 Homocysteine is converted to cystathionine via a transsulfuration pathway that is dependent on the vitamin B₆-dependent enzyme cystathionine β-synthase.6-8 Cystathionine is then converted into cysteine, which is eventually degraded and excreted in the urine. Homocysteine also may be recycled back into methionine by either of 2 remethylation pathways, the most important of
which involves the vitamin B₁₂-dependent enzyme methionine synthase and its co-substrate, 5-methyltetrahydrofolate. The other remethylation pathway is independent of vitamin B₁₂ and folate but uses betaine as a cofactor.

### CAUSES OF HYPERHOMOCYSTEINEMIA

Hyperhomocysteinemia may result from abnormalities in the function of any of the enzymes involved in homocysteine metabolism or from deficiencies of enzyme cofactors or co-substrates (ie, folate, vitamin B₁₂, or vitamin B₉) (Table 1).

Diminished activity of methionine synthase or 5-methyltetrahydrofolate reductase because of genetic abnormalities, vitamin deficiencies, or medication use may cause hyperhomocysteinemia. Indeed, the most common form of genetic hyperhomocysteinemia results from production of a thermolabile variant of 5-methyltetrahydrofolate reductase with decreased activity. Homozygosity for this mutant enzyme is present in 9% to 17% of the population, and heterozygosity can be detected in 30% to 41% of the population. Homocystinuria is a rare disorder, heterozygous deficiency of this enzyme is present in 9% to 17% of the population. Homocystinuria is a rare disorder, heterozygous deficiency of this enzyme is present in 9% to 17% of the population, and heterozygous deficiency of this enzyme is present in 9% to 17% of the population.

### Table 1. Causes of Hyperhomocysteinemia

<table>
<thead>
<tr>
<th>Enzyme deficiencies</th>
<th>Cystathionine β-synthase</th>
<th>Methionine synthase</th>
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<tr>
<td>5-Methyltetrahydrofolate reductase</td>
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<td>Vitamin deficiencies</td>
<td>Folate</td>
<td>Vitamin B₁₂</td>
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<td>Vitamin B₉</td>
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<tr>
<td>Demographics</td>
<td>Increasing age</td>
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</tr>
<tr>
<td>Men</td>
<td>Tobacco use</td>
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<td>Solid organ transplant recipients</td>
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<td>Chronic medical disorders</td>
<td>Renal dysfunction</td>
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<td>Systemic lupus erythematosus</td>
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<td>Malignant neoplasm</td>
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<td>Psoriasis</td>
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<td>Acute-phase response to systemic illness</td>
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<td>Medication use</td>
<td>Methotrexate</td>
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<td>Nitrous oxide</td>
<td>Antiseizure agents (phenytoin and carbamazepine)</td>
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<td>Nicotinic acid</td>
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<td>Colestipol</td>
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<td>Thiazide diuretics</td>
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### Table 2. Pathophysiological Findings of Hyperhomocysteinemia

<table>
<thead>
<tr>
<th>Endothelial cell injury</th>
<th>Impaired endothelium-dependent vasodilation</th>
<th>Impaired endogenous tissue-type plasminogen activator activity</th>
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<tr>
<td>Increased smooth muscle proliferation</td>
<td>Increased platelet aggregation</td>
<td>Increased synthesis of thromboxane A₂</td>
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<tr>
<td>Decreased synthesis of prostacyclin</td>
<td>Abnormalities of the fibrinolytic</td>
<td>Activation of factors V, X, and XII</td>
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<tr>
<td>Inhibition of antithrombin III</td>
<td>and factor C</td>
<td>Enhanced lipoprotein(a) binding to fibrin</td>
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<td>Correlation with fibrinogen levels</td>
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**HYPERHOMOCYSTEINEMIA AND ATHEROSCLEROSIS**

The vascular and hematologic abnormalities associated with hyperhomocysteinemia lead to a proatherogenic and prothrombotic metabolic milieu (Table 2). These abnormalities include (1) endothelial cell injury, the initial event in the development of atherosclerosis, manifested as impaired endothelium-dependent vasodilation and impaired endogenous tissue-type plasminogen activator activity; (2) increased platelet aggregation, related to increased synthesis of thromboxane A₂ and decreased synthesis of prostacyclin; and (3) abnormalities of the clotting cascade, such as activation of factors V, X, and XII, and inhibition of natural anticoagulants, such as anti-
HYPERHOMOCYSTEINEMIA: EPIDEMIOLOGICAL FINDINGS AND ASVD RISK

Several studies have demonstrated strong associations between hyperhomocysteinemia and CAD (especially premature CAD),5,7,17,22-24,31,50-53 cerebrovascular disease,5,45,50-53 and peripheral arterial vascular disease.5,45,50,53

One of the earliest studies that related hyperhomocysteinemia and ASVD was conducted in Dublin, Ireland.5 Hyperhomocysteinemia, defined as a tHcy level greater than the high threshold level of 24 mmol/L, was more predictive of ASVD than any other risk factor.5 After adjustment for hypercholesterolemia, hypertension, and tobacco abuse, hyperhomocysteinemia was associated with an overall odds ratio (OR; lower limits of 95% confidence limits) for ASVD of 1.39.

In the Physicians’ Health Study, 14,916 male physicians without known ASVD were followed up prospectively for 5 years.50 Plasma tHcy levels were higher in the 271 patients with myocardial infarction than in healthy controls, and the adjusted risk for the highest fifth percentile was 3.1.46 These data were verified by the Framingham Heart Study of 1041 patients, in which the OR of having significant carotid artery stenosis was 2.0 for patients with tHcy levels greater than 14.4 µmol/L.51 A critical observation in this study was that tHcy elevations within the “normal” range (11.4-14.3 µmol/L) also were associated with increased risk of cerebrovascular disease (OR=1.6).51 Furthermore, the risk of significant carotid artery stenosis was associated with decreasing folate levels.51

Recently, the European Concerted Action Project50 addressed the interaction between hyperhomocysteinemia and conventional risk factors for ASVD in a study of 750 case and 800 control patients younger than 60 years.50 The risk for ASVD in patients in the highest quintile of tHcy levels (≥12 µmol/L) relative to the lower quintiles was 2.2. The risk of increasing tHcy levels was continuous, and a 5-µmol/L increment in the tHcy level was associated with an OR for ASVD of 1.3 for men and 1.4 for women. The magnitude of increased risk of ASVD associated with hyperhomocysteinemia was greater than that associated with hypercholesterolemia (OR=1.4), less than that for hypertension (OR=3.9), and similar to that for tobacco use (2.2). For both sexes, the ASVD risk associated with hyperhomocysteinemia was multiplicative in the presence of tobacco use or hypertension.50

The association between CAD and decreasing folate levels also has been verified in several studies.7,17,22,23,31 Significant but less consistent and less powerful associations between CAD and low levels of vitamins B6 and B12 also have been described.7,17,22,24,31,50

Regarding the CAD risk attributed to homocysteine levels, a recent meta-analysis established that a 5-µmol/L increase in the tHcy level was equivalent to an approximately 0.52-mmol/L (20-mg/dL) increase in the total cholesterol level (ie, 20% increased risk).6 The relative risk for CAD associated with increasing tHcy levels in this meta-analysis was lower than reported in the European Concerted Action Project in which a 5-µmol/L change was equivalent to a 2.22 mmol/L (86 mg/dL) change in cholesterol.50,54

SCREENING FOR HYPERHOMOCYSTEINEMIA

Most clinical laboratories use high-performance liquid chromatography to measure plasma tHcy levels, although some laboratories still use older immunoassays. Although both techniques are sensitive, the newer techniques are more specific. Charges for these assays are typically $45 to $100 per measurement. Blood samples should be collected in tubes containing an anticoagulant such as EDTA and centrifuged within 30 minutes to avoid a false elevation of homocysteine levels due to its release from red blood cells. Accordingly, serum homocysteine measurements have a higher normal range. Samples may then be refrigerated or frozen for several weeks. Free homocysteine levels are not useful clinically.

The “normal” range for fasting tHcy values is approximately 5 to 15 µmol/L. The upper limit of this range, however, should be revised downward because the increased risk of atherosclerosis associated with tHcy levels in this range has been well documented.6,8,17,47,50,51 Certain patients with abnormal homocysteine metabolism may have normal fasting plasma tHcy levels and may require provocative testing (ie, methionine loading) to expose this abnormality.6,8,50 The methionine loading test involves oral administration of 100 mg/kg of methionine and measurement of the plasma tHcy level 6 to 8 hours later.6,50 The European Concerted Action Project50 reported that methionine loading identified an additional 27% of cases, despite a strong correlation between baseline and postload tHcy values. The role of methionine loading in clinical practice is controversial, however, because of its excess cost and time commitment and interindividual variation in the time-to-peak tHcy response to methionine loading. Because most of the recent epidemiological studies that associate hyperhomocysteinemia with ASVD only
measured fasting plasma tHcy levels, maintaining this practice seems reasonable, especially until the clinical utility and cost-effectiveness of methionine loading is established. The sensitivity of fasting plasma tHcy levels for identification of patients at risk for ASVD may be improved by using a lower criterion than that used in the European Concerted Action Project (12 µmol/L).50 However, users of multivitamins containing folic acid, pyridoxine hydrochloride, and cyanocobalamin had a significantly lower risk of all forms of ASVD than nonusers, even after adjustment for conventional risk factors (relative risk, 0.38), and at least some of this effect was attributable to lower tHcy levels. A similar observation was made in the Nurse's Health Study, where participants who used moderate doses of vitamin supplements containing folate and pyridoxine had fewer coronary events than nonusers.55

Therapy with folic acid at doses of 400 µg or more daily has been associated with a 30% to 42% decrease in tHcy levels.56-57 Doses lower than this do not result in a sustained reduction in tHcy levels.6,56 Cyanocobalamin supplementation has been associated with a less dramatic reduction in tHcy levels of approximately 15%.56 In the absence of vitamin B12 deficiency, pyridoxine hydrochloride supplementation does not lower tHcy levels significantly.33,36 Combination therapy with all 3 of these vitamins, administered orally or as a monthly intramuscular injection, has been associated with 15% to 72% reductions in tHcy levels.5,12,26,38 It is doubtful that pyridoxine hydrochloride or cyanocobalamin supplementation has an additional homocysteine-lowering effect in addition to folic acid supplementation in patients without deficiencies of these vitamins.56 The US Food and Drug Administration recently mandated fortification of flours and cereal products with 140 µg of folic acid per 100 g. This intervention is expected to have a population effect of lowering tHcy levels by an average of approximately 3 µmol/L and may potentially prevent 17 000 deaths due to ASVD each year.45,59

The safety of folic acid supplementation has been well documented.59,60 Exacerbation of vitamin B12 deficiency has been reported rarely and only occurs with higher doses of folic acid (≥10 mg/d).50 Although folic acid supplementation may mask the red blood cell macrocytosis associated with vitamin B12 deficiency, the red blood cell mean corpuscular volume is an insensitive indicator of vitamin B12 deficiency, and more reliable indicators of vitamin B12 status are available, such as direct measurement of vitamin B12 and methylmalonic acid levels.60 Furthermore, folic acid supplementation does not mask the neurologic or cutaneous manifestations of vitamin B12 deficiency, exacerbate seizure disorders, interfere with effectiveness of antifolate medications, or increase the risk of cancer.60

**SUMMARY OF RECOMMENDATIONS**

In the absence of clinical trial evidence that treatment of hyperhomocysteinemia decreases the risk of ASVD or its clinical manifestations, therapy for this disorder is based on the strong epidemiological association between increasing tHcy levels and ASVD and on the safety and low cost of folic acid supplementation. There is also preliminary evidence that vitamin therapy may prevent progression of cerebral atherosclerosis.51 The optimal dose, combination, and route of administration of homocysteine-reducing therapies have not yet been clarified. Because of these limitations, the following recommendations (Figure 2) were formulated to provide a safe and effective strategy for addressing hyperhomocysteinemia in high-risk patients until clinical trials addressing these issues are completed.

For the primary prevention of ASVD, screening for hyperhomocysteinemia should be considered in patients at risk for this disorder and for patients at high risk for ASVD who may benefit from homocysteine-lowering therapy (Table 3). Special attention should be given to patients who smoke tobacco or have hypertension because of the asso-

<table>
<thead>
<tr>
<th>Table 3. Screening for Hyperhomocysteinemia*</th>
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<tr>
<td>Atherosclerotic vascular disease without conventional risk factors</td>
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<tr>
<td>Premature atherosclerotic vascular disease (before age 60 y)</td>
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<tr>
<td>High risk for premature atherosclerotic vascular disease</td>
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<tr>
<td>First-degree relative with premature atherosclerotic vascular disease</td>
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<td>Tobacco use</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Chronic renal failure</td>
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<tr>
<td>Unexplained deep venous thrombosis</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Severe psoriasis</td>
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<tr>
<td>Solid organ transplant recipients</td>
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<tr>
<td>Use of homocysteine-raising medications (see Table 1)</td>
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*Defer screening until 8 to 12 weeks after serious systemic illness.
Two weeks after initiation of homocysteine-lowering therapy. If elevated levels persist despite therapy as described above, the dose of the folate acid supplement may be increased to 2000 µg/d, with another measurement of the tHcy level after 6 to 8 additional weeks. Higher doses of folate acid (up to 5000 µg/d) may be needed for patients with end-stage renal disease or continuing sources of folate acid loss. If hyperhomocysteinemia persists, cyanocobalamin supplementation (400 µg/d), even in the absence of overt deficiency, may be beneficial. Although it is an uncommon disorder, vitamin B12 deficiency should be considered in patients with marked hyperhomocysteinemia (tHcy level ≥ 24 µmol/L) or who are refractory to folate acid therapy.

Although estrogen replacement and penicillamine therapies have reduced tHcy levels in small studies, therapy with these medications for the sole purpose of reducing homocysteine levels cannot be recommended. Administration of betaine, a choline derivative that functions as a cofactor in the non–vitamin B12-dependent remethylation pathway of homocysteine metabolism, effectively lowers tHcy levels in patients with homocystinuria who are unresponsive to pyridoxine hydrochloride supplementation and may prevent arterial and venous thrombotic events in these patients. Use of this orphan drug in patients with less severe hyperhomocysteinemia is not recommended because of its expense and the availability and effectiveness of the therapies described above.

These recommendations for screening and treating patients with hyperhomocysteinemia, for the purposes of preventing AVSD and its complications, may be modified when more epidemiological data and prospective clinical trial data, such as from the Heart Protection Study II, become available. Until then, these conservative recommendations provide a safe, effective, and evidence-based approach to the diagnosis, evaluation, and management of patients with hyperhomocysteinemia.

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Reprints: James H. Stein, MD, University of Wisconsin Medical School, 600 Highland Ave, H6/315 CSC, Madison, WI 53792 (e-mail: jhs@medicine.wisc.edu).

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