Overview of homocysteine

INTRODUCTION — Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. Homocystinuria or severe hyperhomocysteinemia is a rare autosomal recessive disorder characterized by severe elevations in plasma and urine homocysteine concentrations. Clinical manifestations of homocystinuria include developmental delay, osteoporosis, ocular abnormalities, thromboembolic disease, and severe premature atherosclerosis. Homocystinuria is not discussed further in this topic review.

Less marked elevations in plasma homocysteine are much more common, occurring in 5 to 7 percent of the population [1,2]. Although unassociated with the clinical stigmata of homocystinuria, mounting evidence suggests that moderate hyperhomocysteinemia is an independent risk factor for atherosclerotic vascular disease and for recurrent venous thromboembolism.

This topic will review the risks associated with elevated homocysteine levels, screening for hyperhomocysteinemia, and the evidence evaluating the use of vitamin supplements that lower homocysteine levels.

ETIOLOGY OF HYPERHOMOCYSTEINEMIA — Homocysteine is metabolized by one of two divergent pathways: transsulfuration and remethylation (figure 1). The transsulfuration of homocysteine to cysteine is catalyzed by cystathionine-ß-synthase, a process that requires pyridoxal phosphate (vitamin B6) as a cofactor. Remethylation of homocysteine produces methionine. This reaction is catalyzed either by methionine synthase or by betaine-homocysteine methyltransferase. Vitamin B12 (cobalamin) is the precursor of methylcobalamin, which is the cofactor for methionine synthase.

Elevations in the plasma homocysteine concentration can occur due to genetic defects in the enzymes involved in homocysteine metabolism, to nutritional deficiencies in vitamin cofactors, or to other factors including some chronic medical conditions and drugs (figure 1) [3-9]. Some drugs used in the treatment of hypercholesterolemia, such as fibrates and nicotinic acid, can raise homocysteine levels by approximately 30 percent; however, the clinical significance of this is uncertain [10-12]. Cigarette smoking also may elevate homocysteine levels [13]. Chronic kidney failure can increase homocysteine levels due to decreased renal removal and impaired metabolism. (See "Secondary prevention of cardiovascular disease in end-stage renal disease (dialysis)", section on 'Hyperhomocysteinemia'.)

Thermolabile variant of MTHFR — The most common form of genetic hyperhomocysteinemia results from production of a thermolabile variant of methylene tetrahydrofolate reductase (MTHFR) with reduced enzymatic activity (T mutation) (figure 1) [14]. The gene encoding for this variant contains a cytosine to thymine substitution at nucleotide 677 (C677T) [15].

The responsible gene is common, with a population frequency estimated between 5 to 14 percent [16,17]. Homozygosity for the thermolabile variant of MTHFR (TT genotype) is a relatively common cause of mildly elevated plasma homocysteine levels in the general population, often occurring in association with low serum folate levels [17-19]. As an example, one study of 625 men found that 11.5 percent were homozygous for the TT genotype [18]. However, for those in the top 5 and 10 percent of plasma homocysteine concentrations, the frequency rose to 48 and 36 percent, respectively. Homozygotes also had the lowest serum folate concentrations.
Vitamin deficiencies — Increased blood levels of homocysteine may reflect deficiency of folate, vitamin B6, and/or vitamin B12 [20-23]. Plasma folate and B12 levels, in particular, are strong determinants of the homocysteine concentration. Homocysteine levels are inversely related to folate consumption, reaching a stable baseline level when folate intake exceeds 400 µg/day [24,25]. Vitamin B6 is a weaker determinant [25].

The importance of vitamin deficiency in the pathogenesis of hyperhomocysteinemia was evaluated in a cohort of 1041 elderly subjects [24]. Two-thirds of patients with elevated homocysteine levels had a subnormal plasma concentration of folate, vitamin B12, or pyridoxal-5-phosphate (the coenzyme form of vitamin B6). The prevalence of low plasma B12 levels was higher in this cohort than in the younger participants in a European case-control study [25]. These data suggest that suboptimal B12 intake coupled with poorer absorption might play a greater role in elevating homocysteine and subsequent CHD risk in older adults than in younger patients. In contrast, folate intake low enough to raise plasma homocysteine may be relatively common in the general population, particularly in moderate consumers of alcohol.

Further evidence of the importance of vitamin deficiency comes from a report that assessed the results of the United States Food and Drug Administration regulation requiring all enriched grain products be fortified with folic acid. Patients who had blood tested following fortification had significantly higher blood folate concentrations and lower homocysteine concentrations [26]. In addition, the prevalence of a high homocysteine concentration (>13 µmol/L) decreased from 18.7 before fortification to 9.8 percent after fortification.

Additional support for the role of folic acid and perhaps vitamin B6 in hyperhomocysteinemia comes from a trial that randomly assigned 158 healthy siblings of 167 patients with premature atherothrombotic disease to folic acid (5 mg daily) and vitamin B6 (250 mg daily) or placebo; most of the siblings and all of the patients had postmethionine loading hyperhomocysteinemia [23]. After a two-year follow-up, fasting and postmethionine homocysteine levels significantly decreased with vitamin supplementation, from 14.7 to 7.4 µmol/L and 64.9 to 34.9 µmol/L respectively, while there were no changes with placebo therapy.

ATHEROTHROMBOTIC PROPERTIES OF HOMOCYSTEINE — Homocysteine has primary atherogenic and prothrombotic properties. Histopathologic hallmarks of homocysteine-induced vascular injury include intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, marked platelet accumulation, and the formation of platelet-enriched occlusive thrombi [27-31]. These observations may help explain the association between hyperhomocysteinemia and cardiovascular disease described below.

There are multiple mechanisms by which homocysteine may induce vascular injury:

- Homocysteine promotes leukocyte recruitment by upregulating monocyte chemoattractant protein-1 and interleukin-8 expression and secretion [32].
- The thiolactone metabolite of homocysteine can combine with LDL-cholesterol to produce aggregates that are taken up by vascular macrophages in the arterial intima; these foam cells may then release the lipid into atherosclerotic plaques [2].
- Homocysteine increases smooth muscle cell proliferation and enhances collagen production [33].
- Prothrombotic effects of homocysteine, which have been demonstrated in patients with acute coronary syndromes [34], include attenuation of endothelial cell tissue plasminogen activator binding sites, activation of factor VIIa and V, inhibition of protein C and heparin sulfate, increased fibrinopeptide A and prothrombin fragments 1 and 2, increased blood viscosity, and decreased endothelial antithrombotic activity due to changes in thrombomodulin function [35-40]. (See "Overview of hemostasis").
- Oxidative stress by free radicals formed during the oxidation of reduced homocysteine may directly injure endothelial cells [41,42].
- Marked platelet accumulation may be secondary to direct proaggregatory effects of homocysteine or to an impairment in endothelium-mediated platelet inhibition [43,44].
• Prolonged exposure of endothelial cells to homocysteine reduces the activity of dimethylarginine dimethylaminohydrolase, the enzyme that degrades asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase; this impairs the production of nitric oxide. This may contribute to impaired endothelium-dependent vasodilation of both conduit and resistance vessels. (See “Coronary artery endothelial dysfunction: Clinical aspects”.)

Support for the role of homocysteine in endothelial dysfunction is derived from studies that found that folic acid supplementation both lowers the homocysteine concentration and improves measures of endothelial dysfunction.

An alternate view is that hyperhomocysteinemia is not directly harmful, but that it indirectly inhibits methyl fluxes during transmethylation of methionine; the resulting impairment of DNA methylation could then affect many physiologic processes. A study in patients with uremia and hyperhomocysteinemia found increased levels of DNA hypomethylation and altered gene expression that were corrected by administration of folate.

LABORATORY DIAGNOSIS — Sensitive assays allow quantification of the total plasma homocysteine concentration; approximately 75 to 85 percent is protein-bound and 15 to 25 percent is in acid-soluble free forms. Normal homocysteine concentrations range between 5 and 15 µmol/L. Hyperhomocysteinemia has been classified as follows:

- Moderate (15 to 30 µmol/L)
- Intermediate (30 to 100 µmol/L)
- Severe (>100 µmol/L)

An oral methionine challenge (100 mg/kg) can be given to patients suspected of hyperhomocysteinemia who have normal fasting homocysteine levels. The oral methionine challenge is more useful for patients with cystathionine-beta-synthase deficiency than for those with MTHFR reductase deficiency. The homocysteine concentration is measured on fasting samples before the methionine challenge and four and eight hours afterward. The patient is classified as having impaired homocysteine metabolism if the four hour post-methionine plasma homocysteine concentration exceeds the appropriate mean level by more than two standard deviations.

However, the prognostic significance of the oral methionine challenge is uncertain. In one series that included 26 subjects who were homozygous for the thermolabile variant, fasting but not postmethionine total homocysteine levels were associated with CHD status.

Homocysteine levels measured at the time of admission for acute myocardial infarction and unstable angina appear to be accurate. In this small study, levels at admission were similar to those six months after the acute event, but there were minor variations in the homocysteine level during the first week after admission.

ROLE IN VASCULAR DISEASE

Hyperhomocysteinemia — Although early data on the relationship between elevated blood homocysteine concentrations and coronary heart disease (CHD) and stroke have been somewhat inconsistent, high homocysteine levels appear to be clearly associated with an increased risk of cardiovascular and cerebrovascular disease. However, homocysteine does not appear to be as important as other risk factors such as hypercholesterolemia, smoking, diabetes mellitus, and hypertension. (See "Overview of the possible risk factors for cardiovascular disease", section on 'Vitamins, antioxidants and homocysteine'.)

A meta-analysis that evaluated data from 30 prospective and retrospective studies, involving 5073 ischemic heart disease and 1113 stroke events, provides an analysis of the varied data. Stronger associations between the blood homocysteine concentration and cardiovascular events were noted in retrospective compared with prospective studies. After adjustment for known cardiovascular risk factors, a 25 percent lower homocysteine concentration (about 3 µmol/L) in the prospective studies was associated with a lower risk of ischemic heart disease risk (odds ratio 0.89, 95% CI 0.83-0.86) and stroke (odds ratio 0.81, 95% CI 0.69-0.95).
These results are supported by a meta-analysis of 40 observational studies involving 11,162 patients who were homozygous for the thermolabile variant of MTHFR and 12,758 matched controls [65]. Patients with the MTHFR TT genotype had a 16 percent higher odds of coronary heart disease compared with controls (odds ratio 1.16, 95% CI 1.05-1.28). Additionally, the MTHFR TT genotype is associated with an increased risk of silent brain infarcts [66].

A meta-analysis performed for the US Preventive Services Task Force specifically examined the issue of whether homocysteine levels add predictive value for determining the risk of CHD in adults without known CHD [67]. The analysis found that, independent of Framingham risk factors, each increase in homocysteine level of 5 µmol/L increases the risk of CHD events by approximately 20 percent.

Hyperhomocysteinemia has been linked to the following vascular events:

- Myocardial infarction, other acute coronary syndromes, and recurrent coronary events [34,68-74]
- Premature coronary heart disease [71,75,76]
- Cardiovascular and total mortality [74,77-79]
- Adverse outcomes after angioplasty [80]
- Carotid artery stenosis (figure 2) [81-83]
- Stroke [84-88], recurrent stroke [89], and silent brain infarct [90]

Homocysteine levels have also been linked to the development of heart failure. A community-based cohort study found that higher homocysteine levels increased the risk of heart failure even after controlling for interim myocardial infarctions [91].

The issue of whether homocysteine plays a causal role in cardiovascular disease or whether there is a non-causal association has additionally been addressed by meta-analyses that have looked at both prospective studies and MTHFR mutation studies [92,93]. Similar odds ratios for cardiovascular disease were found in both types of studies. The consistent odds ratios across studies that should have had distinct sources of bias and error argue in favor of a causal role for homocysteine [94]. In contrast, a subsequent meta-analysis of MTHFR mutation studies found no evidence of a causal relationship between homocysteine and coronary heart disease in studies of North American, European, and Australian populations, but did find such evidence in studies of Middle Eastern and Asian populations [95]. The study found evidence of publication bias, and the authors felt the results could potentially be explained by such bias or by geographic variability in folate intake.

**Vitamin status** — Studies have also contributed to our knowledge regarding the complex relationship between the blood homocysteine concentration, vitamin status, and the risk of cardiovascular disease:

- In a case-control study that evaluated 750 patients with documented vascular disease and 800 control subjects, low levels of folate and vitamin B6 were associated with an increased risk for atherosclerosis, independent of conventional risk factors [20]. The risk associated with folate was in part explained by increased serum homocysteine, while the relationship between vitamin B6 and atherosclerosis was independent of the homocysteine concentration.

- The Nurses' Health Study found a graded inverse association between higher dietary intakes of folate and vitamin B6 and CHD [21]. The lowest risk was seen in women in the highest quintile of intake for both folate and vitamin B6 (40 percent risk reduction). This lowest risk group had a dietary intake of folate above 545 micrograms/day and an average intake of vitamin B6 above 5.9 mg/day, which are well above the current RDAs (400 micrograms/day and 1.6 mg/day, respectively) (figure 3). The benefits of folate supplementation were greatest in women consuming the most alcohol, probably because alcohol increases folate metabolism and these women were relatively deficient to start. No association was observed between dietary vitamin B12 and CHD.

- The Health Professional Follow-up Study of 43,732 men ages 40 to 75 who were free of cardiovascular disease and diabetes at baseline found in a multivariate analysis that compared with men in the lowest
quintile of folate intake, men in the highest quintile had a relative risk of ischemic stroke of 0.71 (95% CI 0.52-0.96) [96]. No significant association was found between hemorrhagic stroke and folate intake. Intake of vitamin B12, but not vitamin B6, was also inversely associated with the risk of ischemic stroke.

- An association between dietary folate and atherosclerosis was demonstrated in a prospective study of 1980 men, ages 42 to 60 years, who were followed for 10 years [22]. Those in the highest quintile of folate intake (>297 µg/day, mean intake 342.1 µg/day) had a relative risk of an acute coronary event of 0.45 compared to those in the lowest quintile (<211 µg/day, mean intake 187.7 µg/day); there was no association with B6 intake and only a weak association with the B12 intake.

- In the meta-analysis of MTHFR mutations discussed above, there was significant heterogeneity between studies performed in European compared with North American populations, with a significant association between the TT genotype and coronary disease in the former but not the latter [65]. This heterogeneity may be explained by differences in folate status; the North American studies were performed after 1995, at a time when there was greater use of B vitamin supplements and folate fortification. Thus, adequate folate status appears to minimize the effect that the MTHFR TT genotype has on risk of cardiovascular disease. Another possible explanation is the difference in vitamin B2 (riboflavin) fortification in North America and Europe. A randomized trial found that vitamin B2 supplementation lowered homocysteine levels in patients with the MTHFR TT genotype but not in those with other genotypes [97].

- Low levels of vitamin B6 may be independently associated with CHD [98]. After adjusting for other risk factors, higher plasma concentrations of pyridoxal 5'-phosphate were associated with a lower incidence of CHD; the relative risk for the highest versus lowest quintile was 0.28. This is supported by the data from a multicenter European study that showed that vitamin B6 was directly related to CHD risk independent of homocysteine levels [25]. Vitamin B6 may be more effective in counteracting the effects of methionine loading (simulating the fed state) on homocysteine levels, while folate may be more important in regulating plasma homocysteine in the fasting state [99,100].

Data from studies are somewhat inconsistent, however. As an example, an Australian cohort study of 2950 people followed for 29 years that did not measure homocysteine concentration found no independent association of baseline serum folate, red cell folate, and serum vitamin B12 concentrations with mortality from cardiovascular disease after adjusting for age and other standard risk factors [101].

ROLE IN VENOUS THROMBOEMBOLISM — There is increasing evidence that hyperhomocysteinemia is a risk factor for venous thromboembolic disease (pulmonary embolism and deep vein thrombosis) [102-104]. Meta-analyses of case-control studies have found an odds ratio of 2.5 to 2.95 for venous thromboembolic disease in patients with homocysteine levels more than two standard deviations above the mean value of control groups [103,104].

Moderate hyperhomocysteinemia (15 to 30 µmol/L) may also be a risk factor for recurrent venous thrombosis. This was illustrated in a multicenter study in which patients with a single episode of idiopathic venous thromboembolism were prospectively followed after discontinuation of oral anticoagulants [105]. Recurrent venous thromboembolism was significantly more likely in the 66 patients with hyperhomocysteinemia than in the 198 with normal levels (18.2 percent versus 8.1 percent, respectively).

Some studies have suggested that the risk of thrombosis increases 10 to 50-fold in patients who have both homocysteinemia and an inherited thrombophilia (eg, factor V Leiden) (see "Factor V Leiden and activated protein C resistance: Clinical manifestations and diagnosis") [106,107]. However, other studies have failed to confirm these findings [108]. These contradictory results may reflect statistical anomalies due to the small number of patients that have both defects. Further confusing the issue, most studies that have examined patients with the thermolabile variant of MTHFR have not found that this genotype increases the risk of venous thrombosis when found alone [109-111], or when associated with factor V Leiden or the prothrombin mutation [108,110].
Overview of homocysteine

Obstetric complications — The thermolabile variant of MTHFR has been linked to obstetric complications such as severe preeclampsia, abruptio placenta, fetal growth restriction, and stillbirth, which are associated with intervillous or spiral artery thrombosis and inadequate placental perfusion [112]. Women with an obstetric complication were significantly more likely to have the thermolabile variant of MTHFR. (See "Screening for inherited thrombophilia in asymptomatic individuals").

ROLE IN OTHER CONDITIONS

Birth defects — Supplementation with folate reduces the risk of neural tube defects. (See "Vitamin supplementation in disease prevention", section on 'Folic acid'.) Homozygosity and heterozygosity for the thermolabile variant of MTHFR appear to be associated with an increased risk of neural tube defects [113].

Osteoporosis — Homocystinuria is associated with the early onset of osteoporosis. (See "The child with tall stature and/or abnormally rapid growth"). High homocysteine levels in adults have been associated with osteoporotic fractures in some [114-117], but not all [118], studies.

Supplementation with folate and vitamin B12 in high risk groups may reduce the risk of fractures [119]. (See "Overview of the management of osteoporosis in postmenopausal women", section on 'Other therapies'.)

It is not clear, however, whether high levels of homocysteine have a direct effect on bone or whether the effect is mediated through another factor, such as poor nutrition.

Dementia — There is conflicting evidence about whether homocysteine is an independent risk factor for dementia. (See "Risk factors for cognitive decline and dementia", section on 'Homocysteine'.)

SCREENING FOR HYPERHOMOCYSTEINEMIA — The bulk of data suggest that hyperhomocysteinemia is an independent risk factor for cerebrovascular, peripheral vascular, and coronary heart disease, and for venous thromboembolic disease. However, this relationship alone does not provide a compelling argument for population screening [120]. The arguments against screening in the general population include the following:

- Identifying patients with the TT genotype of MTHFR is unlikely to be cost-effective. Combining the prevalence of the TT genotype (approximately 11 percent) and the relative risk, it is possible to estimate the population attributable risk (the proportion of coronary heart disease that would be eliminated from the population if the genetic variant did not exist) [121]. For the TT genotype, the population attributable risk is only 1 to 2 percent. In addition, adequate folic acid intake further reduces the impact of the genetic variant.

- While screening for hyperhomocysteinemia itself is not difficult, a benefit from lowering the homocysteine concentration on cardiovascular and venous thromboembolic disease remains unproven (see 'Treatment' below) [103,122]. Thus, even if we identify patients with an elevated homocysteine concentration it is not clear that acting on this information is of benefit.

- Even if treatment of hyperhomocysteinemia is beneficial, it may be more cost effective to recommend that people take a daily multivitamin. (See "Vitamin supplementation in disease prevention".)

Additionally, measurement variability of homocysteine is a significant problem in determining appropriate candidates for treatment [123].

Several randomized clinical trials are underway to address the effect of folate, B6, and B12 supplementation in primary prevention of cardiovascular disease.

Until the results of these studies are available, and given the negative results of using supplementation for secondary prevention, we recommend not screening for hyperhomocysteinemia. (See 'Secondary prevention' below.)

TREATMENT — There is no high quality evidence from trials with clinical endpoints to support treating patients who do not have severe hyperhomocysteinemia (homocystinuria).
The majority of hyperhomocysteinemia is caused by low levels of folate and vitamin B12 in patients with or without the thermolabile variant of MTHFR [124]. Correcting nutritional inadequacy of folic acid, vitamin B12, and choline (betaine) will lower homocysteine levels [124]. A diet rich in fruits, vegetables, and low-fat dairy products and low in saturated and total fat also can lower fasting serum homocysteine [125].

In patients who are treated beyond diet, the treatment varies with the underlying cause, but generally involves vitamin supplementation with folic acid, vitamin B12, and vitamin B6.

**Lowering homocysteine levels** — Vitamin supplementation with folate lowers homocysteine levels. In patients who are treated to lower homocysteine levels, we suggest treating with folic acid (1 mg/day), vitamin B6 (10 mg/day), and vitamin B12 (0.4 mg/day). All patients should receive a B complex vitamin to mitigate against peripheral neuropathy. Normalization of the homocysteine concentration has been reported within two weeks, but further lowering of homocysteine levels occurs by six weeks [126]. The dose of folic acid should be increased up to 5 mg/day as needed to lower the homocysteine concentration below 15 µmol/L. In patients with a homocysteine concentration >30 µmol/L or chronic renal failure the initial dose of folic acid is 5 mg/day.

The effect of dose and treatment duration was illustrated in a study in which 37 otherwise normal subjects with persistent hyperhomocysteinemia were treated with 0.2 mg/day of folic acid [17]. The plasma homocysteine concentration was reduced in almost all within seven weeks and fell to the normal range in 21 by seven months; most of the remaining subjects attained normal homocysteine concentrations on a higher folate dose of 5 mg/day.

Supplementation with folate has shown the following dose-response relationships in patients with CHD:

- In a review of 75 patients, cereal providing 127 µg of folic acid daily increased plasma folic acid by 31 percent and reduced homocysteine by 3.7 percent [127]. Cereals providing 499 and 665 µg of folic acid per day raised plasma folic acid by 65 and 106 percent, respectively and lowered plasma homocysteine by 11 and 14 percent, respectively.

- In the PACIFIC trial, 723 patients were randomly assigned to folic acid (2.0 or 0.2 mg/day) or placebo [128]. The fall in serum homocysteine was significantly greater at the higher dose (16 versus 11 percent, 1.8 versus 1.2 µmol/L).

Although the data are limited, in refractory cases we begin therapy with trimethylglycine (betaine) 750 mg twice daily and increase the dose as necessary.

**Secondary prevention**

**Cardiovascular disease** — Meta-analyses of randomized clinical trials for supplementation aimed at lowering homocysteine levels in patients with established cardiovascular disease demonstrated somewhat controversial results [129-133]. However, most studies have generally found no decrease in cardiovascular events or death.

In one of the largest trials included in these meta-analyses, the HOPE-2 trial, 5522 patients ages 55 and older with known vascular disease or diabetes were randomly assigned to receive supplementation with folic acid 2.5 mg daily, vitamin B6 50 mg daily, and vitamin B12 1 mg daily, or to receive placebo [134]. Mean homocysteine levels decreased by 2.4 µmol/L in patients in the supplement group and increased by 0.8 µmol/L in the placebo group. After a mean follow-up of five years, treatment with supplementation had no effect on the primary combined endpoint of cardiovascular death, myocardial infarction, and stroke (relative risk 0.95, 95% CI 0.84-1.07). There was also no benefit in patients with higher baseline homocysteine levels.

Although these results make it unlikely that reducing homocysteine levels with B-vitamin supplement is beneficial for the prevention of cardiovascular disease, it remains possible that design of the trials could have led to a benefit being missed. Most trials did not assess for overt homocysteinemia and adequate nutritional conditions, particularly folate and other B-vitamins. This limits the power of trials to detect benefits, particularly in populations that consume foods fortified with folate [54]. The above trials were performed in regions with a high
folate concentration in the population and also included many patients without elevated homocysteine levels. In addition, control subjects received daily vitamin mixtures containing folic acid. It is noteworthy to find marked effects on homocysteine concentration due to the thermolabile MTHFR as well as in the probability for stroke in a population low in folate consumption, such as Asian countries, compared with areas in the folate fortification [135]. Trials performed in the future that target a specific homocysteine level in patients with baseline hyperhomocysteinemia, or that dose supplements to achieve specific serum folate or vitamin B12 levels, might be able to demonstrate clinical benefit.

In summary, the current trials found no benefits, even in the subsets of patients with elevated homocysteine levels at baseline. In the absence of demonstrable benefit and the absence of trials looking at subsets of patients with much more elevated homocysteine levels, we recommend not treating hyperhomocysteinemia for secondary prevention in patients with cardiovascular disease.

**After PCI** — In the specific case of supplementation after percutaneous coronary intervention (PCI), there is conflicting evidence:

- A randomized trial of a daily combination supplement (folic acid 1 mg, vitamin B12 400 mcg, vitamin B6 10 mg) in 553 patients undergoing PCI found a decreased incidence of major adverse events after an average follow-up of 11 months [136]. The risk for a composite end point (death, nonfatal myocardial infarction, need for repeat revascularization) was significantly lower in patients receiving the supplement than in those receiving a placebo (15.4 percent versus 22.8 percent) primarily due to a reduced rate of target lesion revascularization (9.9 percent versus 16.0 percent). There was a trend toward fewer deaths (1.5 versus 2.8 percent, relative risk 0.54 [95% CI 0.16-1.70]) and toward fewer nonfatal myocardial infarctions (2.6 versus 4.3 percent, relative risk 0.60 [CI 0.24 to 1.51]). Only 29 percent of the patients had baseline elevated homocysteine levels (above 12 µmol/L) and none had severe hyperhomocysteinemia (above 100 µmol/L).

- In contrast, a randomized trial of supplementation after coronary stent placement found that patients in the treatment group had higher rates of restenosis (34.5 versus 26.5 percent) and a higher percentage required target-vessel revascularization (15.8 versus 10.6 percent) [137]. Supplementation consisted of an initial intravenous bolus injection of folic acid 1 mg, vitamin B12 1 mg, and vitamin B6 5 mg, followed by daily oral administration of folic acid 1.2 mg, vitamin B12 60 mcg, and vitamin B6 48 mg. In subset analyses, there was a trend toward lower rates of restenosis in women, patients with diabetes, and patients with homocysteine levels of 15 µmol/L or more. The applicability of these results to patients who have received drug-eluting stents, which greatly reduce rates of stent restenosis, is unknown.

The explanation for these conflicting results in PCI is uncertain; however, in the first study only about half the patients received stents. The authors of the second study suggest that supplementation may promote smooth muscle proliferation and matrix formation, which are important parts of restenosis after stenting. Lowering of homocysteine may play a protective role on the thrombus formation within intimal cracks and vascular remodeling that are important after balloon angioplasty [137]. Additionally, the second study used different doses of vitamins and gave an initial intravenous bolus of folic acid 1 mg, vitamin B12 2 mg, and vitamin B6 4 mg, followed by daily oral administration of folic acid 1.2 mg, vitamin B12 60 mcg, and vitamin B6 48 mg. In subset analyses, there was a trend toward lower rates of restenosis in women, patients with diabetes, and patients with homocysteine levels of 15 µmol/L or more. The applicability of these results to patients who have received drug-eluting stents, which greatly reduce rates of stent restenosis, is unknown.

The various trials discussed above used differing doses of folate, vitamin B6, vitamin B12. One possible interpretation of the results is that high level supplementation with vitamin B6 and/or vitamin B12 is harmful while high dose folate supplementation might be beneficial. However, given the generally negative results in secondary prevention, the one trial showing a benefit may have found these results by random chance.

At this point, there is inadequate evidence for benefit. We do not recommend the use of vitamin supplements to lower homocysteine levels in patients with CHD including in patients who have recently undergone PCI.

**Venous thrombosis** — As discussed above, hyperhomocysteinemia is a risk factor for venous thromboembolic
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However, randomized trials have not found benefits on rates of VTE with vitamin therapy:

- A randomized trial examined the role of homocysteine lowering with daily B vitamins (folic acid 5 mg, vitamin B6 50 mg, vitamin B12 0.4 mg) in 701 patients with a first episode of VTE [139]. There was no statistically significant reduction in recurrent VTE in patients treated with B vitamins (hazard ratio [HR] 0.84, 95% CI 0.56-1.26). There was also no reduction in recurrent VTE in the 360 patients with baseline homocysteine levels above the 75th percentile (HR 1.14, CI 0.65-1.98), or in the 341 patients with normal homocysteine levels (HR 0.58, CI 0.31-1.07).

- A secondary analysis from the HOPE-2 trial, described above (see 'Cardiovascular disease' above), found no effect of vitamin therapy on rates of VTE (HR 1.01, CI 0.66-1.53) [140]. Vitamin therapy also did not appear to be effective in the 821 patients with a baseline homocysteine in the highest quartile in the study (>13.8 µmol/L), however, the confidence intervals were wide (HR 1.71, CI 0.48-6.06).

Based on these data, we suggest not screening for or treating hyperhomocysteinemia in patients with VTE.

SUPPLEMENTATION IN THE GENERAL POPULATION — Several large randomized clinical trials of vitamin B6, vitamin B12, and folate for the primary prevention of cardiovascular disease and stroke are underway [141]. These studies include large numbers of subjects and various doses and combinations of vitamins and will likely guide future recommendations for supplementation.

Until the results of these trials are available, decisions about the utility of supplementation in the general population must be based on extrapolation from observational data showing associations between homocysteine levels, vitamin levels, and vascular disease (see 'Vitamin status' above); from data from interventional trials showing the effects of supplementation on homocysteine levels; and from secondary prevention trials. It is uncertain whether relatively short-term trials of supplements in secondary prevention apply to long-term treatment for primary prevention, but with several other forms of therapy (eg, statins, hormone replacement) effects in primary prevention appear similar to those first demonstrated in secondary prevention.

A meta-analysis assessed the effects of supplementation in 12 trials with 1114 people [142]. Folic acid in a dose of 0.5 to 5.0 mg/day lowered serum homocysteine by 25 percent (95% CI 23-38 percent); vitamin B12 at 0.5 mg/day provided an additional reduction of 7 percent (95% CI 3-10 percent), while vitamin B6 had no additional effect (however, this study did not consider homocysteine levels after methionine loading). A similar effect of folic acid has been noted in subsequent clinical trials [127,128,143]. The effect would be expected to be less in patients with lower baseline serum homocysteine and higher baseline serum folate [128]. One report found that a folic acid dose of 0.8 mg/day was necessary to achieve the maximum reduction in serum homocysteine concentration [143].

In the absence of stronger evidence, and given the lack of benefit in secondary prevention trials, we do not recommend vitamin supplementation for the purpose of lowering homocysteine levels for primary prevention of cardiovascular disease. (See 'Secondary prevention' above.)

SUMMARY AND RECOMMENDATIONS — Hyperhomocysteinemia appears to be an independent risk factor for cerebrovascular, peripheral arterial, and coronary heart disease, and for venous thromboembolic disease. However, it does not appear to be as important as other cardiovascular risk factors such as hypercholesterolemia, smoking, diabetes mellitus, and hypertension.

- We suggest not screening for hyperhomocysteinemia, including in patients with otherwise unexplained venous thrombosis (Grade 2B). (See 'Screening for hyperhomocysteinemia' above and 'Venous thrombosis' above.)

- We recommend that patients with cardiovascular disease NOT be treated with vitamin supplementation aimed at lowering homocysteine levels (Grade 1B). (See 'Secondary prevention' above.)
● We suggest that patients with venous thrombosis NOT be treated with vitamin supplementation aimed at lowering homocysteine levels (Grade 2B). (See ‘Venous thrombosis’ above.)

● Given the negative results in secondary prevention, we suggest NOT administering vitamin supplementation for the purpose of lowering homocysteine levels for primary prevention (Grade 2B). (See ‘Supplementation in the general population’ above.)

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Overview of homocysteine


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121. Wilson PW. Homocysteine and coronary heart disease: how great is the hazard? JAMA 2002; 288:2042.
a randomized controlled trial. JAMA 2002; 288:973.


Homocysteine is metabolized by one of two divergent pathways: transsulfuration; and remethylation. The transsulfuration of homocysteine to cysteine is catalyzed by cystathionine-β-synthase (CBS), a process that requires pyridoxal phosphate (vitamin B6) as a cofactor. Remethylation of homocysteine produces methionine. This reaction is catalyzed either by methionine synthase or by betaine-homocysteine methyltransferase. Vitamin B12 (cobalamin) is the precursor of methylcobalamin, which is the cofactor for methionine synthase.

Graphic 72986 Version 3.0
Plasma homocysteine response to methionine challenge

<table>
<thead>
<tr>
<th>Gender</th>
<th>Baseline</th>
<th>4 hours</th>
<th>8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6.2</td>
<td>16.3</td>
<td>17.5</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>6.3</td>
<td>14.7</td>
<td>17.6</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>4.8</td>
<td>22.4</td>
<td>24.7</td>
</tr>
</tbody>
</table>

Plasma homocysteine levels (mean plus two standard deviations, in µmol/L) at baseline and four and eight hours after an oral methionine load in men and women. Homocysteine metabolism is considered to be impaired if values above these levels are obtained.


Graphic 79494 Version 1.0
Homocysteine and carotid stenosis

Age-adjusted prevalence of extracranial carotid artery stenosis (>25 percent) in 1041 elderly men and women in the Framingham Heart Study according to the plasma homocysteine concentration. The trends toward a higher frequency of carotid stenosis at increasing homocysteine levels was statistically significant. The individual data points represent the different quartiles for homocysteine.

Women with the highest intake of folate and alcohol have the lowest risk for coronary heart disease

The relative risk of coronary heart disease (nonfatal myocardial infarction and fatal coronary heart disease) by quintiles of folate intake across levels of alcohol consumption among 80,082 women in the Nurses' Health Study. Women in the lowest quintile of folate who did not drink alcohol were the reference category (relative risk 1.0). The benefits from increasing amounts of folate intake are seen primarily in women who consume alcohol and the benefit increases as alcohol consumption increases.


Graphic 51335 Version 3.0
Disclosures

Disclosures: Robert S Rosenson, MD  Grant/Research/Clinical Trial Support: Amgen [Lipids (Evolocumab)]; Sanofi [Lipids (Alirocumab)]; AstraZeneca [Lipids (Evolocumab)]; Genzyme [Lipids (Epanova)]; Sanofi [Lipids (Mipomersen)]; GlaxoSmithKline [Lipids (Alirocumab)]. David S Kang, MD  Trial Support: Regeneron [LDL cholesterol treatment (alirocumab)]; Sanofi [LDL cholesterol treatment (alirocumab)]. David M Rind, MD  Employee of UpToDate, Inc. Equity Ownership/Stock Options (Spouse): Bonfire Development Advisors [CBT (iCBT)].

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