Homocysteine and Cardiovascular Disease

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Editors' Note: *This month we continue the new feature—STEPped Care: An Evidence-Based Approach to Drug Therapy. These articles are designed to provide concise answers to the drug therapy questions that family physicians encounter in their daily practice. The format of the feature will follow the mnemonic STEP: safety (an analysis of adverse effects that patients and providers care about), tolerability (pooled drop-out rates from large clinical trials), effectiveness (how well the drugs work and in what patient population[s]), and price (costs of drug, but also cost-effectiveness of therapy).*[1] *Hence, the name STEPped Care.*

Since the informatics pioneers at McMaster University introduced evidence-based medicine,[2] *Slawson, Shaughnessy, and Bennett*[3,4] *have brought it to mainstream family medicine education and practice. This feature is designed to further the mission of searching for the truth in medical practice. Authors will provide information in a structured format that allows the readers to get to the meat of a therapeutic issue in a way that can help physicians (and patients) make informed decisions. The articles will discourage the use of disease-oriented evidence to make treatment decisions. Examples of disease-oriented evidence include blood pressure lowering, decreases in hemoglobin A_{1c}, and so on. We will include studies that are POEMs—patient-oriented evidence that matters (myocardial infarctions, pain, strokes, mortality, etc)—with the goal of offering patients the most practical, appropriate, and scientifically substantiated therapies. Number needed to treat to observe benefit in a single patient will also be included as a way of defining advantages in terms that are relatively easy to understand.*[5,6]

At times this effort will be frustrating. Even as vast as the biomedical literature is, it does not always support what clinicians do. We will avoid making conclusions that are not supported by POEMs. Nevertheless, POEMs should be incorporated into clinical practice. The rest is up to the reader. Blending POEMs with rational thought, clinical experience, and importantly, patient preferences can be the essence of the art of medicine.

We hope you will find these articles useful and easy to read. Your comments and suggestions are welcome. You may contact the editors through the editorial office of JABFP or on the Internet (http://clinic.isu.edu/drugsteps/intro.html). We hope the articles provide you with useful information that can be applied in everyday practice, and we look forward to your feedback.

Rex W. Force, PharmD, *STEPped Care Feature Editor*
John P. Geyman, MD, *Editor*
Journal of the American Board of Family Practice

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Cardiovascular disease is the leading cause of death in the United States. There are several known risk factors, including family history, age, sex, obesity, diabetes, hypertension, tobacco abuse, and hyper cholesterolemia; however, these alone do not fully explain the pathogenesis associated with cardiovascular disease. In some patients with few or no risk factors, other causes, including hyperhomocysteinemia, might account for the increased risk of atherosclerotic disease.

Hyperhomocysteinemia was first hypothesized to be linked with atherosclerosis more than 25 years ago by Kilmer McCully, when he observed extensive atherosclerotic disease in young patients who had elevated homocysteine concentrations as a result of inborn errors of metabolism.[1] Homocysteine is a sulfur-containing amino acid derived from the demethylation of dietary me-

Submitted, revised, 11 August 1998.

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Supported in part by Missouri Heart Association Grant-in-Aid to Kevin Harris, MD.

thionine.[2,3] There are two metabolic pathways for homocysteine: remethylation and transsulfuration. Folate and vitamin B_{12} are involved in remethylation, which converts homocysteine into methionine. Vitamin B_6 is a factor in transsulfuration, which converts homocysteine into cysteine and other products.[4-7] A deficiency in these or any other products required for the metabolism of homocysteine can result in hyperhomocysteinemia. Several theories exist as to how hyperhomocysteinemia is associated with cardiovascular disease, including endothelial injury or dysfunction, free radical-mediated damage, increased factor V and factor XII activity, decreased protein C activation, and inhibition of thrombomodulin expression.[8-10]

The evidence implicating hyperhomocysteinemia as an independent risk factor in the development of atherosclerosis is well established. More than 80 clinical and epidemiologic studies have shown a relation between hyperhomocysteinemia and coronary heart disease (CHD), peripheral vascular disease, stroke, and venous thrombosis.[2] Currently homocysteine concentrations are not measured routinely in clinical practice; however, they can be measured at most clinical laboratories using high-performance liquid chromatography. Charges typically run from $45 to $100 per measurement.[11]

Folic acid appears to be the most powerful homocysteine-lowering agent, and doses below 2 mg appear to be safe. The US Public Health Service (USPHS) recommends that all women of childbearing potential consume a multivitamin containing 400 µg of folic acid daily to help prevent neural tube birth defects.[12] USPHS also states that there is insufficient evidence to consider diet as a sole source of folate intake.[12] More recently, a report from the Institute of Medicine states that all adults should consume 400 µg of folic acid daily, and those older than 50 years should rely on fortified foods or vitamin supplementation to ensure adequate intake of vitamin B_{12}.[13] The US Dietary Association (USDA) estimates that the average amount of folic acid in the American diet is 242 µg/d.[14] One half of the population ingests less than 200 µg/d of folic acid and 80 percent gets less than 400 µg/d.[14] Many women of childbearing potential might receive only 110 to 140 µg/d of folic acid from dietary sources.[15] Effective as of January 1998, the Food and Drug Administration (FDA) has mandated the fortification of grain products with folic acid; 140 µg of folic acid must be added to 100 g of grain product for the label to read "enriched." It has been estimated that the addition of this amount of folic acid would prevent approximately 40,000 deaths annually from CHD.[2]

To date, no prospective, randomized controlled trials exist concerning folic acid in the treatment of elevated homocysteine concentrations with patient-oriented evidence that matters (POEMs) as outcomes. Nevertheless, providers are often forced to make clinical decisions in the absence of outcome data. Often, randomized, controlled clinical trials have not been done and might never be done. This review, therefore, examines (1) the association of elevated homocysteine concentrations with cardiovascular disease and mortality, and (2) the reduction of homocysteine concentrations with folic acid and other B vitamins, utilizing the STEP approach: **s**afety (how safe is folic acid supplementation), **t**olerability (adverse effects of folic acid supplementation), **e**ffectiveness (ability of folic acid to lower homocysteine concentration), and **p**rice (costs associated with folic acid supplementation).

Methods

MEDLINE was searched from January 1990 through April 1998 using the search terms "homocysteine," "folic acid," "pyridoxine," "cyanacobalamin," "cardiovascular disease," "myocardial infarction," and "mortality." Human studies published in English language journals were included. Only prospective studies with more than 500 subjects were reviewed in detail for the epidemiologic data. All of these studies were nested case-control studies, in that they were part of larger prospective studies from which samples were drawn at baseline and stored. Participants were observed with time, and those who had an event are cases and were matched with controls without disease. Homocysteine concentrations were analyzed from the samples for case and control participants only, not the whole cohort. For the treatment of hyperhomocysteinemia, the largest randomized, placebo-controlled trial to date evaluating folic acid, vitamin B_6, vitamin B_{12}, and the combination was selected for review. Other articles were included at the discretion of the authors.

Association of Increased Homocysteine Level With Coronary Artery Disease and Mortality

Prospective Studies

Stampfer and associates[16] conducted a prospective nested case-control study in men aged 40 to 84 years who had no previous myocardial infarction to assess the risk of CHD (nonfatal myocardial infarction or cardiac death) associated with elevated plasma concentration of homocysteine in 542 male participants in the Physicians' Health Study (271 case and 271 control patients). Samples were drawn at baseline, and patients were observed for up to 5 years. The homocysteine concentrations were higher in case patients than in control patients (11.1 ± 4 versus 10.5 ± 2.8 μmol/L, $P = 0.03$). Contrasting patients with homocysteine concentrations in the top 5 percent with those in the lower 90 percent, the relative risk for myocardial infarction was 3.4 (95 percent confidence interval [CI] 1.3 - 8.8) after adjusting for multiple cardiovascular risk factors. These data suggest that the risk does not increase until the 95th percentile of homocysteine concentration is reached (about 15.8 μmol/L). There also was an inverse correlation between homocysteine concentration and intake of vitamins. The authors concluded that high concentrations of plasma homocysteine are associated with an increased risk of myocardial infarction independent of other coronary risk factors.

Another large prospective study supports the association between hyperhomocysteinemia and CHD. Arnesen and colleagues[17] conducted a nested case-control study in 601 participants (123 case and 478 control) aged 12 to 61 years as part of the Tromso Health Study in Norway. Participants were observed for a mean of 4 years. CHD was defined as CHD on hospital discharge and cardiac death. The homocysteine concentration was higher in case participants (with CHD) than in control participants (without CHD) (21.7 ± 4.7 versus 11.3 ± 3.7 μmol/L, respectively, $P = 0.002$). A 4-μmol/L increase in serum homocysteine concentration was associated with a 41 percent increase in risk of CHD (relative risk [RR], 1.41; 95 percent CI, 1.16 - 1.71); the RR was 1.32 (95 percent CI 1.05 - 1.65) after adjustment for multiple cardiac risk factors. This study confirmed that hyperhomocysteinemia is an independent risk factor for CHD. The results of this study differed from that of Stampfer et al[16] in that there did not appear to be a threshold concentration of homocysteine at which events occur. Rather, the effect was linear.

Table 1. Adjusted Odds Ratio of Death from Coronary Heart Disease for Homocysteine Quartile Groups.

Homocysteine Level Mean (μmol/L)	Range (μmol/L)	Odds Ratio (95% CI)
8.77	< 10.25	1.00
11.26	10.25 - 12.32	1.43 (1.07 - 1.92)*
13.56	12.33 - 15.6	1.46 (1.08 - 1.97)*
19.13	> 15.7	2.9 (2.04 - 4.12)*

From Wald et al.[18]
*Statistically significant compared with lowest quartile

Wald and colleagues[18] conducted a prospective nested case-control study as part of the British United Provident Association (BUPA) study. This study included 1358 men aged 35 to 64 (mean age 58) years who were free of CHD at entry. Patients who died of CHD were case patients (n = 229) and were then age-matched to control patients who did not die of CHD (n = 1126). The mean duration of follow-up was 8.7 years (range 5 - 12 years). The results showed that the mean homocysteine concentration was higher in case than control patients (13.1 versus 11.8 μmol/L, respectively; $P < 0.001$). After adjusting for cardiovascular risk factors, the odds ratio (OR) for risk of death from CHD was significantly higher if the homocysteine concentration was greater than 10.25 μmol/L (Table 1). The odds ratio was 2.9 times higher for patients in the top quartile group of homocysteine concentration when compared with patients in the bottom quartile. After adjustment for cardiovascular risk factors, a 5-μmol/L increase in homocysteine concentration was associated with a 33 percent increase in the risk of death from CHD (OR 1.33; 95 percent CI, 1.22 - 1.59). The linear relation was continuous, as was found in the Arnesen et al study.

In addition, Nygard and associates[19] conducted a prospective cohort study in 587 men and women (median age 62 years) with angiographically confirmed CHD to evaluate the relation between plasma total homocysteine concentrations and overall mortality. Patients were observed for a median of 4.6 years. Homocysteine concentration was strongly associated with overall mortality; this relation was also linear. Kaplan-Meier estimates of mortality were 3.8 percent for patients with homocysteine concentration less than 9 μmol/L, 8.6 percent for homocysteine concentration 9 to 14.9 μmol/L, and 24.7 percent for those with homocys-

teine concentrations of 15 μmol/L or more ($P < 0.001$ for trend). After adjustment for cardiovascular risks, the mortality ratio was significantly elevated only with homocysteine concentrations of 20 μmol/L or higher. As homocysteine concentrations increased, the mortality ratio increased ($P = 0.02$ for trend). After adjustment for sex and age, the strongest predictors of mortality were homocysteine concentration, left ventricular ejection fraction less than 50 percent, and serum creatinine. In this study, elevated plasma homocysteine concentrations were a strong predictor of mortality in patients with angiographically confirmed coronary artery disease. Folate and B_{12} concentrations were not related to mortality, extent of coronary artery disease, or myocardial infarction.

Not every study found an association between homocysteine and CHD. As part of the Multiple Risk Factor Intervention Trial (MRFIT), a nested case-control study was done in 712 men aged 35 to 57 years to evaluate the association between homocysteine and nonfatal myocardial infarction and CHD death.[20] Serum samples were drawn and frozen for up to 20 years, and then analyzed for homocysteine concentration. Nonfatal myocardial infarctions occurred within 7 years after sample collection, but most of the CHD deaths occurred more than 11 years after sample collection. The results of this study showed no association of homocysteine concentration with CHD, even after controlling for other cardiovascular risk factors.

Some potential reasons for the conflicting results of this trial exist. First, because the samples were collected 7 to 11 years before the cardiovascular event, diet and folic acid or multivitamin supplementation could have been different at that time. Diet and folic acid or multivitamin intake were not measured or controlled for, as they were in many other studies. Second, it is unknown whether samples are altered after being frozen for 20 years. Third, the time between sample collection and event was the longest of any of the aforementioned studies. It is possible that the homocysteine concentration started to increase only a few years before the cardiovascular events rather than during the 11 to 20 years of elapsed time before CHD death in this study. Fourth, the MRFIT trial has the potential for selection bias. Health-conscious volunteers were enrolled in this study, and the event rates were much lower than expected. In this study, systolic and diastolic blood pressure, total cholesterol, and lipid subfractions were also not associated with CHD, which is also contradictory to other studies.

Retrospective Studies

Numerous retrospective studies have shown a strong association between hyperhomocysteinemia and CHD.[21-29] An elevated plasma homocysteine concentration has been established as a strong and independent risk factor associated with all categories of atherosclerotic disease, similar to that of smoking or hyperlipidemia. Although the concentration of homocysteine at which the risk begins to increase is unclear and varies between studies, it appears that homocysteine concentrations of greater than 15 μmol/L are most consistently associated with increased CHD risk. Elevated homocysteine concentrations also powerfully increase the risk associated with smoking and hypertension.[30]

Safety and Tolerability of Folic Acid Supplementation

There are very few adverse effects of folic acid supplementation. Nevertheless, some potential toxicities exist. The primary concern is that in patients with undiagnosed vitamin B_{12} deficiency, folic acid supplementation might mask the anemia and result in neurologic complications from the untreated deficiency.[31,32] These toxicities of folic acid appear to be dose-dependent, and a safety threshold of 1 mg/d has been suggested.[31,33] Widespread use of 2 mg/d or more has not resulted in documented morbidity, however.[31] Populations at risk for vitamin B_{12} deficiency are the elderly, vegetarians, those with malabsorption disorders, and patients with acquired immune deficiency syndrome.[12,32] In these patients, and if signs and symptoms of anemia appear, a vitamin B_{12} concentration should be considered before folic acid supplementation. In the studies that evaluated folic acid supplements (1 - 10 mg/d) to lower homocysteine concentrations, all doses were well tolerated.[34-42]

Effectiveness

There is a strong association between hyperhomocysteinemia and the development of CHD. Although no prospective, randomized controlled trials are available showing that lowering homocysteine concentrations with folic acid reduces CHD morbidity or mortality, data indicate that folic acid can lower homocysteine concentration,

Table 2. Relative Risk (RR) of Coronary Heart Disease (Nonfatal Myocardial Infarction and Fatal Coronary Heart Disease) With Folate and Vitamin B Intake, by Quintile.

	1 < 190 µg	2 190 - 244 µg	3 245 - 318 µg	4 319 - 544 µg	5 ≥ 545 µg	*P* Value for Trend
Folate, median, µg/d	158	217	276	393	696	
Cases	237	197	197	168	140	
Multivariate RR (95% CI)	1.0	0.76 (0.63-0.91)*	0.72 (0.60-0.87)*	0.61 (0.50-0.75)*	0.53 (0.43-0.65)*	< 0.001
Vitamin B_6, median, mg/d	1.1	1.3	1.7	2.7	4.6	
Cases	216	210	207	175	131	
Multivariate RR (95% CI)	1.0	0.92 (0.76-1.12)	0.86 (0.70-1.05)	0.88 (0.76-1.10)	0.67 (0.53-0.85)*	= 0 .002

Adapted from Rimm et al.[43]
*Statistically significant compared with quintile[1]

and high folic acid intake has been associated with reduced coronary events.

Lowering Homocysteine Concentrations With Folic Acid Supplementation

Several small studies have shown that folic acid supplementation (0.650 - 10 mg/d) consistently reduces homocysteine concentrations.[34-41] Vitamin B_{12} also decreases homocysteine concentration, but it is not as effective as folic acid.[34,41] Vitamin B_6 has not been shown to lower homocysteine concentration noticeably.[34,37,40] Combinations of folate, vitamin B_6, and vitamin B_{12} are also effective.[34-36,38,40]

Folic acid is the primary component of vitamin combinations that reduce homocysteine. One large randomized placebo-controlled study was done in 100 white men between 20 and 73 years who had homocysteine concentrations greater than 16.3 µmol/L.[34] Patients were randomly assigned for 6 weeks to supplementation with folic acid (650 µg/d), vitamin B_{12} (0.4 mg/d), vitamin B_6 (10 mg/d), a combination of the three, or placebo. Results showed that folic acid, vitamin B_{12}, and vitamin B_6 supplementation reduced plasma homocysteine concentrations by 41.7 percent ($P < 0.001$), 14.8 percent ($P < 0.01$), and 4.5 percent (P = NS), respectively. The combination of the vitamins reduced plasma homocysteine by 49.8 percent ($P = 0.001$), but the combination was not significantly better than folic acid supplementation alone ($P = 0.48$). The authors concluded that the homocysteine-lowering effect of a multivitamin combination containing folate, vitamin B_{12}, and vitamin B_6 is primarily due to its folic acid content. Although the 650 µg/d of folic acid evaluated in this study is higher than the dose in a multivitamin (400 µg), enriched grains and other foods could provide the remainder.

Although the FDA has mandated folic acid fortification in enriched grain products, whether the amount will be sufficient to lower homocysteine concentrations is unknown. Malinow and colleagues[42] conducted a prospective, randomized, double-blind, placebo-controlled, crossover trial in 75 men and women aged 45 to 85 (mean 64) years with documented CHD who were not taking multivitamins or folic acid supplements. Baseline homocysteine concentrations ranged from 1.9 to 27.3 µmol/L. The participants were divided into three groups. Groups A, B, and C received specially prepared breakfast cereals (30 g) containing 127 µg, 499 µg, or 665 µg of folic acid, respectively, or placebo cereal daily for 5 weeks. The treatment cereal also contained vitamin B_6 (1.8 mg) and vitamin B_{12} (6.1 µg) per serving (30 g), which is approximately the amount in a multiple vitamin.

Results showed that homocysteine concentrations were lowered in those in groups A, B, and C by 3.7 percent ($P = 0.24$), 11 percent ($P < 0.001$), and 14 percent ($P = 0.001$), respectively. Concentrations in group A were significantly less than they were in groups B and C, and groups B and C had concentration changes that were not significantly different from each other. Homocysteine concentrations declined linearly with increasing folic acid concentrations ($r = 0.28$; $P = 0.016$), but were not correlated with vitamin B_6 or B_{12} concentrations.

In conclusion, the amount of folic acid that the FDA requires to add to grain products (140 µg/100g) does not appear to be sufficient to lower homocysteine concentrations significantly. Higher

Table 3. Unanswered Questions Concerning Homocysteine and Coronary Heart Disease (CHD).

- Is CHD morbidity and mortality reduced when homocysteine concentrations are lowered with folic acid and other vitamins?
- Is there a benefit in both primary and secondary prevention?
- Does the homocysteine level interact with known modifiable risk factors for CHD?
- What dose of folic acid is optimal for reducing homocysteine?
- When and in whom should homocysteine levels be evaluated?

amounts of folic acid are needed. Because more than 499 µg/d did not offer any additional benefit, a multivitamin (providing 400 µg) daily plus dietary folic acid should be sufficient to lower homocysteine concentration.

Dietary Folate and Vitamin B_6 and Risk of Coronary Heart Disease Among Women

Rimm and colleagues[43] conducted a prospective cohort study in 80,082 women aged 34 to 59 years without CHD in the Nurses Health Study to examine dietary intakes of folate and vitamin B_6 (by food frequency questionnaire) in relation to the incidence of nonfatal myocardial infarction and fatal CHD. There were 658 and 281 cases of nonfatal myocardial infarction and fatal CHD, respectively. Patients were divided into quintiles according to folate intake; each quintile was also evaluated for vitamin B_6 intake. The results are summarized in Table 2. After controlling for multiple cardiac risk factors, the relative risk of CHD was 0.55 (95 percent CI 0.41 - 0.74) among the highest quintile of both folate and B_6 intake compared with the lowest. The risk of CHD was reduced among women who regularly use multivitamins (4 - 7 pills per week) (RR of CHD = 0.76; 95 percent CI, 0.65 - 0.90). Vitamin B_6 concentrations were evaluated under folic acid quintiles; therefore, it is difficult to assess its effect as an individual supplement. The benefits associated with vitamin B_6 are likely linked with the co-administration of folate. The authors concluded that the intake of folate and vitamin B_6 above the current recommended dietary allowance might be important in the primary prevention of CHD among women, and the current dietary recommendations are too low. They suggest folic acid supplementation of 400 µg/d. This study was limited by the lack of homocysteine concentrations. The data are strictly observational, and only an association and no cause-effect conclusion can be made.

Price

Folic acid (average 400 µg/d) is extremely inexpensive. A generic multivitamin contains this dose, and costs $12 - $14 for a full year's supply ($0.03 - $0.04/d)!

Summary

After a thorough review of the available literature, it appears that hyperhomocysteinemia is an independent risk factor for CHD. Furthermore, folic acid has been shown to reduce homocysteine concentration. Nevertheless, CHD is a multifactorial process, and many risk factors play a role in its pathogenesis. Several unanswered questions remain regarding the role of folic acid supplementation in hyperhomocysteinemia (Table 3). The absolute homocysteine concentration at which cardiovascular risk increases is not certain, and the magnitude of homocysteine-lowering needed to prevent events is unknown. Consequently, the number needed to treat cannot be calculated for folic acid supplements. Based on these data, the populations in whom to evaluate a homocysteine concentration have yet to be described.

Because the POEMs are not yet available, it is unknown whether supplemental folic acid to lower homocysteine concentration will reduce CHD morbidity and mortality. It will take several years before any randomized, controlled trials are done, and primary prevention trials will need to be of very long duration to show any change in out-

Table 4. STEPs Overview Quick Read: Use of Folic Acid to Reduce Homocysteine Concentrations.

Safety	Very low risk of adverse effects with folic acid. Only known potential risk is masking a vitamin B_{12} deficiency, which occurs at higher folic acid doses (1-2 mg/d).
Tolerability	Folic acid was very well tolerated in studies evaluating 1-10 mg/d.
Effectiveness	Folic acid is effective in lowering homocysteine concentration. The effect on cardiovascular morbidity and mortality is not yet known.
Price	Very inexpensive ($0.03 - $0.04/d).
Summary	Although outcome data are not yet available, a multivitamin containing 400 µg of folic acid should be considered for patients with documented coronary heart disease and cardiovascular risk factors, and in women of childbearing potential.

comes. Widespread use of folic acid supplementation has been recommended, however, and the need for clinical outcomes might be precluded. Even in the absence of outcome data, the potential benefits of using folic acid appear to outweigh any risks. A diet high in folic acid should be encouraged in everyone (Table 4).

The FDA-mandated folic acid fortification of enriched grain products is most likely insufficient to lower homocysteine concentrations meaningfully, and a daily multivitamin that contains 400 μg of folic acid should be considered for patients who have documented CHD (especially when other risk factors are absent or in patients with premature atherosclerosis) and men and women who have cardiovascular risk factors, in addition to women of childbearing potential. Folic acid supplementation in the form of a multivitamin once daily is safe and inexpensive and might prevent the development and progression of CHD.

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