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Homocyst(e)ine and Coronary Heart Disease

Pharmacoeconomic Support for Interventions to Lower Hyperhomocyst(e)inaemia

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Contents

Abstract

Homocyst(e)ine, a sulphur-containing amino acid, is an intermediate formed during the metabolism of the essential amino acid methionine. Biological and epidemiological evidence suggest that elevated plasma levels of homocyst(e)ine are a risk factor for atherosclerosis and coronary heart disease (CHD). In the general US population, hyperhomocyst(e)inaemia is common and most often due to mild nutritional deficiencies in the B vitamins (folic acid, vitamin B_{12} and vitamin B_6). While high homocyst(e)ine levels can be effectively lowered using folic acid and other B vitamins, it is unknown whether such vitamin therapy will lead to clinical benefits. Given that strategies for homocyst(e)ine-lowering are safe and inexpensive, however, even small reductions in CHD risk will be highly cost effective. Thus, it may be prudent for patients to ensure an adequate daily intake of dietary folic acid and other B vitamins and for physicians to screen high-risk adults such as those with established CHD as we await definitive results from ongoing clinical trials.

Homocysteine, a sulphur-containing amino acid, is an intermediate formed during the metabolism of the essential amino acid methionine. During the 1960s, it was discovered that rare enzymatic defects in methionine metabolism, which resulted in extremely high plasma levels of homocyst(e)ine (>250 μmol/L) and homocystinuria, were associated with extensive atherosclerosis in young patients.[1-5] In 1969, McCully[6] first suggested hyperhomocyst(e)inaemia as a potential risk factor for atherosclerosis and coronary heart disease (CHD).[6] Biological evidence accumulated over the last 30 years implies a causative role: high homocyst(e)ine levels have been associated with endothelial dysfunction, vascular smooth muscle cell growth, hypertension, pro-oxidant properties, and thrombosis.[7-9] Numerous epidemiological studies have reinforced this link and, importantly, have extended it to even modestly elevated levels of homocyst(e)ine (≥11 μmol/L).[10-14]

In the general US population, hyperhomocyst-(e)inaemia is common and most often due to mild nutritional deficiencies in the B vitamins (folic acid, vitamin B_{12} and vitamin B_6).[11,15,16] Elevated homocyst(e)ine levels can be safely and effectively lowered by replacing nutritional deficiencies in these vitamins.[17] At least nine randomised clinical trials are underway examining whether homocyst(e)ine lowering with supplements of folic acid, vitamin B_{12}, and vitamin B_6 will lower CHD events and mortality. If it does, the potential clinical effects of homocyst(e)ine lowering would be enormous – an estimated 10% of CHD deaths in men and 6% of CHD deaths in women have been attributed to elevated plasma homocyst(e)ine levels in the US.[11] Also, given that folic acid, vitamin B_{12}, and vitamin B_6 are inexpensive, any clinical benefit realised from homocyst(e)ine lowering is likely to be highly cost effective (and, possibly, even cost saving). As of January 1998, the Food and Drug Administration (FDA) mandated fortification of the US food supply with folic acid at 140μg per 100g of cereal. Even at this level of fortification, however, several authorities recommend that supplementation strategies be more widely practiced as we wait for definitive data from clinical trials.[18-20]

In this article, we review evidence linking homocyst(e)ine to CHD, discuss clinical and economic implications of various strategies for managing hyperhomocyst(e)inaemia, and make recommendations for physicians regarding screening and treatment in general and high-risk populations.

1. Homocyst(e)ine Structure, Metabolism, and Measurement

Homocysteine is a sulfhydryl-containing amino acid that is metabolised in humans by two pathways: (i) remethylation and (ii) trans-sulfuration.[9] Remethylation typically occurs through the enzyme methionine synthase, with 5-methyltetrahydrofolate (a derivative of folic acid) as the methyl donor and

vitamin B_{12} as the essential cofactor. Trans-sulfuration, in contrast, occurs through the enzyme cystathionine β-synthase with vitamin B_6 as the essential cofactor. Each pathway accounts for about 50% of homocyst(e)ine elimination, with remethylation determining fasting plasma homocyst(e)ine levels and trans-sulfuration being more important for minimising post-prandial increases.

The term 'homocyst(e)ine' refers to the combined pool of free and protein-bound homocysteine, homocysteine disulfide (homocystine), mixed disulfides, and homocysteine thiolactone measured by common laboratory assays.[21] Most clinical studies investigating the relationship between homocysteine and atherosclerosis have relied on the measurement of total homocyst(e)ine levels, usually in a fasting state or 2 to 6 hours following a standard dose of oral methionine (100 mg/kg). Traditionally, the upper limit of normal for fasting homocyst(e)ine levels is 15 μmol/L, based on epidemiological observations estimating this value as the 95th percentile for the general population.[8] Levels from 15 to 30 μmol/L, >30 to 100 μmol/L, and >100 μmol/L are classified, respectively, as moderately, intermediately, and severely elevated.[7] CHD risk and atherosclerosis have been associated with homocyst(e)ine levels as low as 11 μmol/L. The significance of abnormal homocyst(e)ine levels after methionine-challenge, however, is uncertain.[22]

Although testing was limited to specialized centers in the past, accurate and reliable measurements of homocyst(e)ine are now being performed at community hospitals using newer laboratory techniques. High performance liquid chromatography (HPLC)–based methods remain the gold standard with reported coefficients of variation of 1.1 to 2.8% within batch and 2.1 to 11.4% across batch.[23,24] Costs for HPLC-based assays typically range from $US25 to $US60 per test at the present time (all values in this article are reported in 2001 dollars). Recently developed laboratory techniques including immunoassays (Abbott IMX analyzer®)[25] and enzymatic assays (Catch Incorporated) [personal communication, Glenn Kawasaki, Seattle (WA), 2001 Aug 8] are expected to further increase availability and lower costs.

2. Aetiologies of Hyperhomocyst(e)inaemia

The known causes of hyperhomocyst(e)inaemia are listed in table I and discussed in sections 2.1 to 2.3.

2.1 Genetic Factors

Homocystinuria is a rare metabolic disorder, most commonly caused by a deficiency in the enzyme cystathionine β-synthase and characterised by marked elevations in plasma and urine homocyst(e)ine levels. Patients with homozygous cystathionine β-synthase deficiency typically have homocyst(e)ine levels greater than 250 μmol/L and present at a

Table I. Causes of hyperhomocyst(e)inaemia

Genetic causes
Cystathionine β-synthase deficiency (homocystinuria)
Methylene tetrahydrofolate reductase deficiency
Methionine synthase deficiency
C677 mutation of methylene tetrahydrofolate reductase
Environmental causes
Nutritional deficiencies
Folic acid deficiency
Vitamin B_{12} (cobalamin) deficiency
Vitamin B_6 (pyridoxine) deficiency
Cigarette smoking
Drugs
Methotrexate
Phenytoin
Estrogens
Theophylline
Niacin
Other causes
Advancing age
Male gender
Systemic diseases
Recent myocardial infarction or stroke
Diabetes mellitus
Psoriasis
Hypothyroidism
Malignancies (breast, ovary, pancreas)
Chronic renal insufficiency

young age with abnormalities of the central nervous (mental retardation), skeletal (deformities, osteoporosis), ocular (ectopia lentis), and cardiovascular (venous and arterial thrombosis, premature atherosclerosis) systems.[26] Heterozygotes, estimated at 0.3 to 1% of the general population, have plasma homocyst(e)ine levels in the range of 20 to 40 μmol/L.[9]

Patients with the rare methylene tetrahydrofolate reductase deficiency also have extremely high plasma and urinary homocyst(e)ine levels and develop neuropsychiatric and vascular abnormalities at an early age.[27] Importantly, a more common 'thermolabile' variant of the methylene tetrahydrofolate reductase enzyme – due to a C677T point mutation in the gene resulting in an alanine-to-valine substitution – is present in 5 to 15% of general population groups studied.[28,29] While this variant is associated with mild to moderate elevations in homocyst(e)ine levels especially in association with low folic acid intake,[30] whether it independently increases risk for CHD or atherosclerosis is uncertain.

2.2 Environmental Factors

Environmental factors including nutritional deficiencies, cigarette smoking, and medications have been associated with hyperhomocyst(e)inaemia. Deficiencies in folic acid and vitamin B_{12} – the essential cofactors in homocyst(e)ine metabolism – are common causes of mildly elevated homocyst(e)ine levels in the general population.[15,16] In the Third National Health and Nutrition Examination Survey (NHANES III), two-thirds of cases of hyperhomocyst(e)inaemia were attributed to B vitamin deficiencies, with folic acid intake the strongest predictor of elevated levels.[16] Cigarette smoking is known to interfere with the synthesis of pyridoxine, resulting in lower plasma levels of vitamin B_6 and hyperhomocyst(e)inaemia.[31] Methotrexate, phenytoin, theophylline, and niacin raise homocyst(e)ine levels by interfering with its breakdown at various points in its metabolic pathway.[9]

2.3 Other Causes

Elevated homocyst(e)ine levels are associated with increasing age and male gender.[32] In addition, reports suggest South African Blacks on average have lower homocyst(e)ine levels than Whites[33] and Asian Indians have higher levels than Europeans.[34] Individuals with chronic renal insufficiency, in particular, represent a large group of patients with very high homocyst(e)ine levels and greatly increased risk for CHD.[35] Diabetes mellitus, psoriasis, hypothyroidism, malignancies (breast, ovary, and pancreas) and recent cardiovascular thrombosis have been associated with hyperhomocyst(e)inaemia.[36]

3. Homocysteine and Coronary Heart Disease (CHD): Biological and Epidemiological Evidence

3.1 Biological Evidence

While the exact roles of homocyst(e)ine in the pathogenesis of CHD and atherosclerosis are uncertain, several mechanisms have been demonstrated experimentally. First, direct endothelial toxicity from homocyst(e)ine occurs *in vivo* and in cultured cells[37-39] via several mediators including nitric oxide.[40-42] Elevated homocyst(e)ine levels also generate homocyst(e)ine thiolactone which is known to be toxic to endothelial cells.[43] In animal models, diet-induced hyperhomocyst(e)inaemia has led to impairments in endothelial vasodilatation and atherosclerotic vascular lesions.[44] Second, hyperhomocyst(e)inaemia stimulates vascular smooth muscle cell growth, an important step in atherosclerosis.[45,46] Third, elevated homocyst(e)ine levels accelerate the development of high blood pressure in animal models, with supportive epidemiologic findings.[47] Fourth, hyperhomocyst(e)inaemia may have pro-oxidant effects through the generation of hydrogen peroxide and superoxide radicals.[48] Elevated homocyst(e)ine levels have also been linked to the oxidation of low-density lipoprotein (LDL), which promotes atherosclerosis.[49] Finally, hyperhomocyst(e)inaemia affects the coagulation cas-

cade, both directly and indirectly, leading to a prothrombotic state.[50]

3.2 Epidemiological Evidence

Four systematic reviews of the literature on homocyst(e)ine and CHD have recently been published.[11-14] In general, retrospective studies have demonstrated the strongest and most consistent association between hyperhomocyst(e)inaemia and CHD, primarily using case-control designs. A slightly weaker and less consistent association has been seen in prospective reports. On balance, the epidemiological evidence suggests that the relationship between hyperhomocyst(e)inaemia and CHD risk is gradual and linear, with relative risk estimated to increase by 1.3 to 1.4 for a 5 μmol/L increase in homocyst(e)ine.[11,12,19]

3.2.1 Retrospective Studies: Case-Control and Cross-Sectional Studies

Over 30 case-control and cross-sectional studies have examined the association between homocyst(e)ine and CHD, with the majority of studies reporting a statistically significant increased risk of CHD with elevated homocyst(e)ine levels.[11-14] Based on retrospective studies alone, Danesh and Lewington[12] estimated the relative risk for CHD to be between 1.6 and 1.9 for each 5 μmol/L increase in homocyst(e)ine. Important limitations in study design must be considered, however, when interpreting this result. For example, homocyst(e)ine levels may increase following acute vascular disorders such as myocardial infarction and stroke.[51,52] Thus, hyperhomocyst(e)inaemia might be a result – and not a cause – of CHD and atherosclerosis. Retrospective studies are also vulnerable to selection and reporting biases.

3.2.2 Prospective Studies: 'Nested' Case-Control Studies and Cohort Studies

Prospective studies – which assess the presence of a risk factor before disease development – have confirmed an association between hyperhomocyst(e)inaemia and increased CHD risk, although not as consistently as in retrospective studies. In the US Physicians' Health Study, a 3-fold increased risk for myocardial infarction was found after 5 years for men in the top 5% of baseline homocyst(e)ine levels.[53] The British United Provident Association study found a similar relationship: CHD risk was 2.9 times greater in men with homocyst(e)ine levels in the highest quartile compared to those with levels in the lowest quartile after multivariate adjustment.[54] An increased risk of CHD with hyperhomocyst(e)inaemia has been reported in four other prospective studies, including a recent analysis of the Women's Health Study.[55-58] However, findings from prospective studies have not been entirely consistent. An updated analysis of the Physicians' Health Study showed a substantial attenuation in the relationship between hyperhomocyst(e)inaemia and risk for myocardial infarction after 7.5 years of follow-up;[59] furthermore, there was no significant association with angina pectoris and coronary artery bypass surgery in this cohort.[60] In the Multiple Risk Factor Intervention Trial (MRFIT) and the Atherosclerosis Risk in Communities (ARIC) Study, no relationship was found between hyperhomocyst(e)inaemia and CHD after multivariate adjustment.[61,62] Comparisons between prospective studies are complicated by the use of diverse patient populations, differing follow-up time periods, different threshold values for statistical analyses (e.g. contrasting the upper and lower quartiles versus the upper 5% and the lower 95%) and inconsistent methods of adjustment for other CHD risk factors.[13] These issues may explain, in part, inconsistencies seen in the literature. In a meta-analysis of the prospective studies, Danesh and Lewington[12] estimated CHD risk to increase by 1.3 for each 5 μmol/L rise in homocyst(e)ine levels.

Finally, studies performed exclusively in patients with established CHD have found a similar relationship between hyperhomocyst(e)inaemia and future CHD events.[63-66] In a study by Nygard and others,[63] a 1.6 to 2.5-fold increase in mortality was noted for each 5 μmol/L rise in homocyst(e)ine among patients with documented angiographic disease.

4. Population-Based Strategies for Lowering Homocyst(e)ine Levels

Homocyst(e)ine levels may be safely and effectively lowered using the B vitamins either through dietary modification or oral supplementation. Among the B vitamins, folic acid has the greatest homocyst(e)ine-lowering effect.[67] Foods rich in dietary folic acid include fortified cereals, lentils, green leafy vegetables and oranges, while vitamins B_{12} and B_6 are found in chicken, fish, and beef (table II).

Dietary changes alone, however, are not likely to increase circulating levels of the B vitamins significantly.[69] Naturally occurring folic acid (or folate) is conjugated with pteroylglutamate groups making its bioavailability upon ingestion only one half that of an equivalent amount of synthetic folic acid.[70] Furthermore, surveys suggest that US diets are an inadequate source. Data from the Framingham Study indicate that over two-thirds of the elderly in 1988 and 1989 consumed less than 400 μg/day of folic acid, the FDA's Recommended Daily Allowance (RDA).[15] Based on NHANES III results, up to half of US adults had low circulating concentrations of folate.[16] Alternatives to dietary modification such as oral supplementation and food fortification therefore need to be considered.

Table II. Common food sources for the B vitamins[a]

Food	Serving size	Amount
Folic acid		
Fortified breakfast cereals	1 cup	200 to 400μg
Chicken liver	3.5 ounces (99g)	770μg
Lentils	½ cup	180μg
Spinach	½ cup	130μg
Fortified pasta	1 cup	60μg
Fortified white rice	1 cup	68μg
Fortified white bread	1 slice	20μg
Orange juice	1 medium	40μg
Vitamin B_{12}		
Breakfast cereals	1 cup	3-6μg
Tuna	3 ounces (85g)	2.5μg
Chicken	3 ounces (85g)	0.3μg
Fish, flounder	3 ounces (85g)	2.1μg
Roast beef	3 ounces (85g)	2.2μg
Turkey breast	3 ounces (85g)	1.7μg
Skim milk	8 ounces (227g)	0.9μg
Vitamin B_6		
Banana	1 medium	0.66 mg
Salmon	3 ounces (85g)	0.55mg
Chicken	3 ounces (85g)	0.51mg
Turkey	3 ounces (85g)	0.32mg
Vegetable juice	6 ounces (170g)	0.24mg
Beef	3 ounces (85g)	0.24mg
Spinach	½ cup	0.22mg

a Table constructed using data from *http://thriveonline.oxygen.com/nutrition/vitamins/guide.index.html*[68]

4.1 Vitamin Supplementation: Folic Acid, Vitamin B_{12}, and Vitamin B_6

Fourteen intervention studies have demonstrated significant decreases in elevated homocyst(e)ine levels following the daily administration of 500 to 10 000μg of folic acid.[17] In most cases, homocyst(e)ine-lowering reaches a plateau after a daily intake of 400 to 600μg, with an average reduction of 25% (or 3 to 4 μmol/L) expected at this dose. Higher doses of folic acid with or without additional B vitamins are needed to effectively lower levels in certain individuals, particularly those with moderate impairments in renal function.[71] The annual cost for generic over-the-counter supplements with 400μg of folic acid is around $US4 to $US6 per person ($US8 to $US15 per person for supplements with 1000μg).[72]

The addition of vitamins B_{12} and B_6 to folic acid appears to have little impact on further homocyst(e)ine reduction. In a recent meta-analysis, vitamin B_{12} in average doses of 500 μg/day was found to lower homocyst(e)ine levels by just 7% in individuals already on folic acid supplements; no reduction was seen with vitamin B_6.[17] Nevertheless, additional supplementation with the two vitamins might be considered for other reasons. First, the most important (and possibly only) adverse effect of folic acid supplementation is its potential to mask vitamin B_{12} deficiency, a common nutritional deficiency of the elderly that is associated with haematological and neurological com-

plications.[73] Adding vitamin B_{12} to folic acid supplements would virtually eliminate this concern. The dosage is a debatable matter since 4 to 6μg is sufficient for normal requirements, but 200 to 500μg is needed for persons with intrinsic factor deficiency in order to overcome difficulties with intestinal absorption. Second, while vitamin B_6 is not effective at lowering fasting homocyst(e)ine levels, its impact on post-prandial levels might be helpful.[74] One study indicated that low levels of vitamin B_6 are associated with CHD independent of homocyst(e)ine.[75] Vitamin B_{12} in a dose of 100 to 500μg would increase annual costs of supplementation by $US5 to $US12 per person, while 50mg of vitamin B_6 would raise it by $US7 to $US14 per person.[72] Replacement of nutritional deficiencies with oral supplements typically lowers elevated homocyst(e)ine levels in 6 to 8 weeks.

4.2 Food Fortification

To prevent neural tube defects, cereal and grain products in the US have been fortified with folic acid since January 1998 at 140μg per 100g of cereal, a level expected to increase intake in the average adult by an additional 70 to 120 μg/day.[76] While this fortification level effectively raises plasma folate concentrations, its lowering of elevated homocyst(e)ine levels may be incomplete. In a randomised controlled study by Malinow and colleagues,[77] patients fed cereals fortified at the mandated level did not have significant reductions in their homocyst(e)ine levels. However, data from the Framingham population comparing distributions of homocyst(e)ine before and after the January 1998 mandate suggest that the prevalence of hyperhomocyst(e)inaemia in the general population (defined as >13 μmol/L in this study) was reduced by as much as 50%.[78] In addition, the authors noted that, following fortification, the percentage of individuals with hyperhomocyst(e)inaemia was similar among those taking and not taking folic acid supplements. A likely explanation for the discrepancy in these studies is that manufacturers are adding more folic acid than is required to be certain that they are fulfilling current regulations. Results from studies evaluating this possibility have been mixed.[79,80]

Fortification, of course, leads to exposure for the total population, which has stimulated urgent consideration of potential health risks, especially for older adults and those with vitamin B_{12} deficiency. It is hard to find documentation, however, for any serious haematological or neurological complications associated with folic acid supplementation in previously undiagnosed individuals.[81] Nevertheless, to prevent this potentially important adverse effect of folic acid, co-fortification of food products with vitamin B_{12} has been suggested and is currently under evaluation.[11,82] Other adverse effects of widespread food fortification include the possibility that folic acid may inadvertently lower serum levels of common antiepileptics (e.g. phenytoin) or affect absorption of trace minerals (e.g. zinc), although these are less likely at currently suggested levels of fortification.[83,84]

Fortification with folic acid reportedly has minimal effect on the taste, appearance, and shelf-life of common foods.[85] Based on estimates from the FDA, the annual cost of fortifying cereal grains (i.e., flours made from wheat, rice, corn, barley, and rye), rice, farina, and macaroni or pasta is $US4.2 million for the current level of 140μg per 100g and would be $US10.6 million for a higher level of 350μg per 100g.[86] Indirect costs for activities such as analytic testing and label changes add an estimated $US29.2 million.[86] Cost estimates of the adverse consequences of folic acid in persons with undiagnosed vitamin B_{12} deficiency are extremely imprecise and vary widely – from $US43 million[85] to $US2.4 billion[86] per year for the higher fortification level – based on divergent assumptions of its incidence and severity. Given such a considerable level of uncertainty, the FDA remains cautious about mandating further changes in the fortification level – including co-fortification with vitamin B_{12} – until better evidence on the impact of the 1998 standard and data from ongoing clinical trials are obtained and carefully reviewed.

5. Current Status of Randomized Clinical Trials

Nine randomised clinical trials are now underway to evaluate whether lowering high homocyst(e)ine levels with folic acid and other B vitamins reduces the incidence of CHD and other vascular events (table III).[13,87] These trials aim to enroll over 50 000 high-risk subjects (e.g. those with multiple risk factors for CHD or established cardiovascular disease) and, if successful, will be able to detect a 10% relative risk reduction in major cardiovascular events (e.g. death, nonfatal myocardial infarction, and stroke).[13] The impact of folic acid is being assessed in all nine trials in dosages varying from 200 μg/day to 5 mg/day. Vitamins B_{12} and B_6 are being used in various combinations and doses in some of the trials, with several investigators using 2 by 2 factorial designs to assess the individual effects of each vitamin. Two trials are examining the effect of folic acid with omapatrilat (Prevention with A Combined Inhibitor and Folate In Coronary heart disease; PACIFIC) or high-dose statin therapy (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SEARCH). The Women's Antioxidant and Cardiovascular disease Study (WACS) has added folic acid, vitamin B_{12}, and vitamin B_6 to its ongoing examination of the health effects of vitamins C and E in women. A recent analysis by Bostom et al.[88] has cautioned that several of these clinical trials in the general population, particularly in the US and Canada, are likely to be underpowered due to the effects of mandated folic acid fortification on homocyst(e)ine levels among patients in the trials' control arms.

6. Potential Clinical Benefits and Economic Costs of Screening and Treating Hyperhomocyst(e)inaemia with Folic Acid Supplementation

6.1 Supplementation Strategies for Lowering Homocyst(e)ine Levels in the General Population (Primary Prevention)

Previously, we constructed a decision analytic model using clinical and economic inputs from the available literature to estimate the potential bene-

Table III. Current large-scale randomised clinical trials examining the benefits of homocyst(e)ine-lowering[a]

Study name, setting	Sample size	Intervention	Starting date
Western Norway B Vitamin Trial (WENBIT), Norway	2000	Folic acid (5mg x 2wk + 0.8mg) and B_{12} (0.4mg) *vs* placebo; 2 × 2 factorial design with B_6 (40mg) *vs* placebo	1997
Vitamin Intervention for Stroke Prevention (VISP), US	3600	Folic acid (2.5mg), B_{12} (0.4mg), and B_6 (25mg) *vs* folic acid (0.02mg), B_{12} (0.06mg), and B_6 (0.2mg)	1998
Women's Antioxidant and Cardiovascular Disease Study (WACS), US	8000	Folic acid (2.5mg), B_{12} (1mg), and B_6 (50mg) *vs* placebo	1998
Cambridge Heart Antioxidant Study (CHAOS-2), United Kingdom	4000	Folic acid (5mg) *vs* placebo	1998
Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), United Kingdom	12 000	Folic acid (2mg) and B_{12} (1mg) *vs* placebo; 2 × 2 factorial design with simvastatin (80mg *vs* 20 mg)	1998
Norwegian Study of Homocysteine Lowering with B-vitamins in Myocardial Infarction (NORVIT), Norway	3000	Folic acid (5mg x 2wk + 0.8mg) and B_{12} (0.4mg) *vs* placebo; 2 × 2 factorial design with B_6 (40mg) *vs* placebo	1998
Prevention with a Combined Inhibitor and Folate in Coronary Heart Disease (PACIFIC), Australia	10 000	Folic acid (0.2mg or 2mg) *vs* placebo; 2 × 2 factorial design with omapatrilat	1998
Heart Outcomes Prevention Evaluation-2 Study (HOPE-2), Canada	5000	Folic acid (2.5 mg), B_{12} (1 mg), and B_6 (50 mg) *vs* placebo	1999
Vitamins To Prevent Stroke (VITATOPS), Australia	5000	Folic acid (2mg), B_{12} (0.4mg), and B_6 (25mg) *vs* placebo	1999

a Table constructed using data from Eikelboom et al.[13] and Clarke and Armitage.[87]

fits and costs of homocyst(e)ine-lowering in hypothetical cohorts of 40-year-old men and 50-year-old women from the general population.[89] For the base-case analysis, we assumed that: (i) hyperhomocyst(e)inaemia increased the relative risk of CHD-related death by 1.4 for each 5 μmol/L rise in homocyst(e)ine levels;[19] (ii) lowering levels would reduce the relative risk of homocyst(e)ine-associated CHD by 40% (e.g. from 1.4 to 1.24 in those with initial homocyst(e)ine levels of 15 μmol/L or more); and (iii) folic acid had negligible side effects when given with vitamin B_{12}. We evaluated two folic acid supplementation strategies: (i) screening with a fasting homocyst(e)ine level followed by treatment with a daily folic acid (400μg) and vitamin B_{12} (500μg) supplement for those with homocyst(e)ine levels of 11 μmol/L or more (a Screen and Treat strategy) and (ii) no screening before taking a daily folic acid and vitamin B_{12} supplement (a Treat-All strategy). Probabilities of clinical events and cost estimates were obtained from the literature and are listed in table IV. Extensive sensitivity analyses were performed on highly uncertain estimates, including an analysis that varied the level of assumed CHD risk reduction with homocyst(e)ine-lowering from a worst-case scenario (0% risk reduction) to a best-case scenario (100% risk reduction).

Overall, we found Screen and Treat to be more cost effective than Treat-All, with cost-effectiveness ratios (CER) for Screen and Treat ranging from $10 000 to $30 000 per life-year saved when compared with no intervention (table V). Importantly, we found during sensitivity analysis that CERs for Screen and Treat remained favourable (defined arbitrarily as a CER under $50 000 per life-year saved)[90] even when we assumed low levels of CHD risk reduction. Only a 12% risk reduction in men and a 24% risk reduction in women were needed for CERs to remain under $50 000 per life-year saved. This last finding suggests that even if homocyst(e)ine-lowering results in small clinical benefits, population-based screening and treatment would be justified given its low costs. While Treat-All yielded slightly more life-years saved (as expected), its incremental cost per additional life-year saved when compared to Screen and Treat was extremely high – from $680 000 to $1 390 000 – even under worst-case scenarios for the sensitivity, specificity, and cost of the homocyst(e)ine assay. Finally, all our findings of economic favorability were strengthened even more when the model's treatment strategies assumed the use of lower-dose vitamin B_{12} supplements (i.e., less than 500μg) due to decreased costs.

6.2 Supplementation Strategies for Lowering Homocyst(e)ine Levels in Patients with CHD (Secondary Prevention)

We have now re-evaluated the two folic acid supplementation strategies in hypothetical cohorts of men and women with established CHD. For this group of patients, several key model assumptions were made. First, the relative risk of death associated with hyperhomocyst(e)inaemia was estimated at 1.6 for each 5 μmol/L increase in homocyst(e)ine based on the Nygaard study.[63] Second, the distribution of homocyst(e)ine levels in this group of patients was assumed to be similar to its distribution in the general population (a conservative assumption since most data suggest a distribution shifted to higher values in patients with CHD). Finally, age– and gender-specific mortality rates from the CHD Policy Model were used to estimate long-term survival in these individuals with chronic CHD.[91]

Assuming a 40% reduction in CHD risk with effective homocyst(e)ine lowering (as with our previous model), Screen and Treat and Treat-All yielded CERs of $US2660 and $US6100 per life-year saved, respectively, compared with no intervention in men and $US3490 and $US9660 in women (table V). The incremental CERs for Treat-All (when compared with Screen and Treat) were high at $US117 000 per additional life-year saved in men and $US158 000 per additional life-year saved in women. During sensitivity analysis, the CER for Screen and Treat remained under $US50 000 per life-year saved when just a 3% risk reduction in CHD risk was assumed in both men and women.

Table IV. Clinical and economic estimates used in the decision analytic model

Model parameter	Base-case analysis estimates		Range assessed in sensitivity analyses	
	men	women	men	women
Population prevalence of serum homocyst(e)ine levels (%)				
<11 μmol/L	60.5	68.0	50-80	60-80
11-12 μmol/L	9.4	6.9	4.8-11.9	4.3-8.6
12-13 μmol/L	6.4	5.8	3.2-8.1	3.6-7.2
13-14 μmol/L	6.4	5.1	3.2-8.1	3.2-6.4
14-15 μmol/L	4.2	3.7	2.1-5.3	2.3-4.6
≥15 μmol/L	13.1	10.6	6.7-16.6	6.6-13.2
Relative CHD risk for hyperhomocyst(e)inaemia				
<11 μmol/L	1.0	1.0	N/A	N/A
11-15 μmol/L	1.07 per μmol/L	1.07 per μmol/L	N/A	N/A
≥15 μmol/L	1.4	1.4	N/A	N/A
Homocyst(e)ine assay characteristics (%)				
Sensitivity	97	96	80-99	80-99
Specificity	97	98	80-99	80-99
Adherence rate with folic acid (%)	50	50	25-75	25-75
Effectiveness of folic acid at lowering homocyst(e)ine levels <11 μmol/L (%)	50	50	40-67	40-67
Cost of homocyst(e)ine assay ($US, 2001 values)	44.55	44.55	22-107	22-107
Annual cost of supplementation ($US, 2001 values)				
With folic acid and B_{12} (base-case)	17.56	17.56	3-25	3-25
With folic acid	4.75	4.75	3-25	3-25
% Reduction in excess homocyst(e)ine-associated CHD risk after lowering homocyst(e)ine <11μmol/L	40	40	0-100	0-100

CHD = coronary heart disease; **N/A** = not available.

CERs for Screen and Treat remained favourable under additional sensitivity analyses that evaluated the costs of screening and treatment, screening assay characteristics, and the effectiveness of folic acid at homocyst(e)ine lowering.

6.3 Other Studies

Using the well-established CHD Policy Model, Tice and colleagues also estimated the potential benefits and costs of homocyst(e)ine lowering in the general population.[92] This study expands on our earlier analysis by: (i) modelling the impact of the 1998 folic acid fortification standard on baseline levels of homocyst(e)ine in the general population and (ii) evaluating the cost effectiveness of homocyst(e)ine-lowering strategies across various age-groups of patients. Based on their model's results, oral supplementation with folic acid and vitamin B_{12} is likely to remain cost effective even after adjusting for the beneficial effects of current fortification standards – especially in groups with high CHD event rates (e.g. the elderly, men, and those with established CHD).

7. What Should Clinicians Do with Present Knowledge?

First, the lack of definitive data should not be interpreted, in our opinion, as an absence of data. Evidence accumulated over the last 30 years confirms a strong and consistent association between hyperhomocyst(e)inaemia and CHD. Furthermore, observational data suggest that lowering high homocyst(e)ine levels with folic acid and other B vitamins is likely to be beneficial in atherosclerosis.[93,94] Nevertheless, important lessons of the past – e.g. hormone replacement therapy in CHD[95] and

β-carotene in lung cancer and cardiovascular disease[96] – caution us about the potential dangers of relying exclusively on observational studies to evaluate promising new therapies. Any recommendations regarding supplementation with the B vitamins therefore must be necessarily guarded.

Recent guidelines from the American Heart Association (AHA) suggest it is reasonable to screen and treat high-risk individuals (e.g. those with established CHD).[8] For the general population, AHA guidelines recommend an adequate dietary intake of folic acid (400μg), vitamin B_{12} (2.4μg) and vitamin B_6 (1.7mg). Recent reviews by the Canadian Task Force on Preventive Health Care[97] and International Task Force for the Prevention of Coronary Heart Disease[98] leave no final recommendations on screening or treatment, and expert opinions in the literature have been mixed.[18-20,99-102]

Because we interpret the totality of current evidence linking homocyst(e)ine and CHD as credible and feel that treatment with folic acid at a dose of 400μg is safe and inexpensive, we believe that screening adults (40-year-old men and 50-year-old women) in the general population for hyperhomocyst(e)inaemia followed by targeted treatment is a rational and prudent strategy to pursue until ongoing trials are completed. We especially recommend this strategy in high-risk individuals such as those with established CHD or multiple CHD risk factors. For those taking folic acid, we recommend at least 4 to 6μg of supplemental vitamin B_{12} as well. We do not recommend supplemental vitamin B_6 at this time given inadequate data supporting its use

8. Conclusion

Due in large part to remarkable advances in the discovery and treatment of CHD risk factors, US age-adjusted death rates from CHD have declined dramatically over the last four decades.[103] Yet the established risk factors for CHD – age, gender, diabetes mellitus, high blood pressure, smoking, and hyperlipidaemia – explain less than half of its incidence.[104] Cardiovascular diseases continue to account for nearly one million deaths and over $US300 billion in healthcare costs each year in the US.[105] Thus, the search for additional risk factors, especially modifiable ones, remains a key priority for cardiovascular research.

Hyperhomocyst(e)inaemia is a recently recognised risk factor for CHD that can be effectively, safely, and inexpensively lowered with folic acid and other B vitamins. While awaiting hopefully definitive results from ongoing clinical trials, we support dietary choices and FDA-mandated fortification aimed at increasing the daily intake of folic acid and other B vitamins. In addition, we feel it is prudent for physicians to consider screening high-risk adults in the general population and patients with established CHD for homocyst(e)ine levels of 11 μmol/L or more and treating those with hyperhomocyst(e)inaemia using daily oral supplements containing 400μg of folic acid and at least 4 to 6μg of vitamin B_{12}.

Table V. Estimated benefits and costs of folic acid supplementation strategies in the general population and patients with coronary heart disease (CHD) [all costs in $US, 2001 values]

	General population				Patients with CHD			
	Screen and Treat		Treat-All		Screen and Treat		Treat-All	
	men	women	men	women	men	women	men	women
Life-years saved per 1000[a]	8.4	3.7	8.7	3.9	43.7	30.3	45.1	31.6
Cost per person screened and/or treated[a]	$126	$112	$302	$328	$116	$106	$275	$305
Cost per life-year saved[a]	$14 900	$29 900	$34 800	$84 200	$2660	$3490	$6100	$9660
Incremental cost per additional life-year saved[b]	–	–	$680 000	$1 390 000	–	–	$117 000	$158 000

a Compared with no intervention.

b Compared with Screen and Treat.

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