

Cardiovascular Effects of Vitamins: Are They Really “Amines” of Life?

Vitamins are organic molecules not synthesized by the human body but are required for carrying out essential biochemical reactions. The fact that vitamin deficiency causes illness, along with the belief that an excess of the water-soluble vitamins is harmless, has encouraged their over-consumption in the last several decades. This literature review will discuss several of the main prospective studies that were published in the last few years regarding vitamin E, folic acid and vitamins B6 and B12 and their influence on our treatment policy.

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Sophie's routine check-up



Sophie, 57, comes to your office for primary prevention. She has Type 2 diabetes and a strong family history of cardiovascular disease (CVD). She exercises several times a week and follows a healthy diet.

Last year, her homocysteine (Hcy) level was 13.1 $\mu\text{mol/L}$, but decreased to normal (which is $< 8 \mu\text{mol/L}$) after supplementation with folic acid, vitamin B6 and B12.

What would you tell her regarding the supplements?

Her medications include:

- Metformin, 0.5 g, twice daily
- Ramipril, 10 mg, once daily
- Acetylsalicylic acid, 81 mg, once daily
- Folic acid, 5 mg, once daily
- Vitamin B12, B6 and E, once daily
- A multivitamin tablet, once daily
- An organic calcium supplement

She looks fit and is not overweight. Her general physical examination is normal, but her blood pressure (BP) is 140/84 mmHg.

Her blood work shows:

- Fasting blood glucose: 6.5 mmol/L
- HbA1c: 6.5% with normal kidney functions

Her lipid profile shows:

- Total cholesterol: 4.4 mmol/L
- LDL-cholesterol: 2.5 mmol/L
- HDL-cholesterol: 1.4 mmol/L
- Total cholesterol to HDL-cholesterol ratio: 3.2

Sophie is at high risk for developing CVD because of her diabetes. You explain to her that according to the Women's Health Study,⁵ vitamin E had no benefit in the primary and secondary prevention of CVD and might even be harmful.^{4,6,8} More recently, several published studies have put into question the value of other vitamins. The Vitamin Intervention for Stroke Prevention study,¹⁹ Norwegian Vitamin Trial²¹ and Heart Outcomes Prevention Evaluation-TOO²¹ study didn't show any significant benefit to taking Hcy-lowering vitamins (*i.e.*, folic acid and vitamins B6 and B12). These studies also indicated that there may even be harmful effects to taking these supplements.

You congratulate Sophie on her healthy lifestyle but ask her to add a low salt diet and to work towards the BP goal of 130/85 mmHg. She should discontinue taking vitamin E, as well as the Hcy-lowering vitamins because she will not benefit from taking them and there may be harmful effects.

In 1912, Casimir Funk, a Polish biochemist, created the word “vitamine.” *Vita*—in Latin—means life, while the suffix *amine* was actually biochemically inaccurate.

This review will discuss several of the main prospective studies that were published in the last few years regarding vitamin E, folic acid and vitamins B6 and B12 and their influence on our treatment policy.

Vitamin E

Vitamin E is a fat-soluble antioxidant. The fact that free radicals and other oxidative processes can enhance the atherosclerotic progression has led to intense retrospective and later, prospective investigations linking vitamin E to that process.

Early on, epidemiologic studies (including animal models) indicated an inverse relation between vitamin E intake (dietary and/or supplementary) and cardiovascular (CV) risk, which consequently added to its extensive use.¹ In 1997, up to 44% of US cardiologists reported routine use of antioxidant supplements, mainly vitamin E, for the primary prevention of cardiovascular disease (CVD).²

Several randomized controlled trials (RCT)³⁻⁵ and meta-analysis studies,⁶⁻⁸ published early in this decade, did not support these epidemiologic reports.

In 2005, Mills et al⁸ evaluated the potential dose-dependent effect of vitamin E supplementation on all-cause mortality. They reviewed 19 trials that included almost 136,000 participants—most of whom were at high-risk for CVD. No effect of vitamin E on all-cause mortality was found. Analysis of the results, according to vitamin E dosages, (where low is considered < 400 IU and high is > 400 IU) revealed a direct relation: all-cause mortality progressively increased as vitamin E dosage increased (or

was > 150 IU), daily. A non-significant reduction of all cause mortality was found in dosages < 150 IU, daily.

The risk ratios for selected vitamin E dosages were:

- 0.98 for 50 IU,
- 0.99 for 100 IU and 200 IU,
- 1.01 for 200 IU
- up to 1.05 for 500 IU and
- 1.07 for a mega dosage of 1000 IU.

The Heart Outcomes Prevention Evaluation (HOPE) trial,³ published in 2000, didn't find any effect of vitamin E on CV outcomes. This includes:

- CVD,
- death,
- stroke and
- myocardial infarction [MI]

with a daily dosage of 400 IU for an average use of 4.5 years. More than 9,500 high-risk participants (with established CVD or diabetes and another risk factor), older than 55 years of age, were included in this double-blind RCT.

In the HOPE-TOO trial,⁴ (an extension of the first study) the authors assessed the effect of the same daily dosage of vitamin E (400 IU) on the same composite CVD end point and cancer for a total period of seven years. No benefit of taking vitamin E in preventing major CV events (or cancer) was found. Yet, a non-significant increase in heart failure was found in the vitamin E-treated group, along with evidence of decreased left ventricular ejection fraction.

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In 2005, the Women's Health Study (WHS)⁵ was conducted to verify the effect of vitamin E on healthy women. Almost 40,000 healthy women, > 45 years of age, were followed for an average of 10 years. This RCT, in which the women took 600 IU of vitamin E every other day, or placebo every other day, did not reveal any statistically significant benefits on the primary end points of major CV events or cancer. A non-significant reduction in the number of CVD events and CV deaths, which was mainly attributed to fewer sudden deaths in the vitamin E group, was seen.

No benefit to taking vitamin E supplements was observed in a subgroup of women with increased oxidative stress (*i.e.*, smokers, women with dyslipidemia, hypertension and diabetes).

The only significant reduction that was found was in the number of major CV events (MI and CV deaths) among the oldest group of women (RR [relative risk] = 0.74), who were at least 65 years of age when assigned to vitamin E supplements. No effect on total mortality was observed.

The Physicians' Health Study results on vitamin E in healthy men are expected to be published in 2008.

Conclusions regarding vitamin E

Taking vitamin E supplements revealed no statistical benefit in either healthy women or in high-risk patients. Benefits were found only in the subgroup of healthy women > 65 years of age. Even this benefit must be balanced with the concern about harmful CV effects, increase in heart failure and all-cause mortality.

The 2004 American Heart Association (AHA) Science Advisory⁹ did not find any justification for the use of antioxidant vitamin supplementation to reduce or prevent CVD risk in women.^{9,10}

Homocysteine-lowering vitamins

Homocysteine (Hcy) is a sulphur-containing amino acid that is not found in our diet. It is closely related to the essential amino acid methionine. Its role is in generating methyl groups for the cells.

Hcy breaks down in the body by two pathways, which require either folate (B8) or vitamins B6 and B12 as cofactors (Figure 1).

Dietary intake of these three vitamins is the main factor which determines blood-Hcy levels.^{11,12} Changes in blood-Hcy levels could also be secondary to many other factors, as shown in Table 1.

Hcy levels increase throughout the lifecycle seven to 10% every decade^{13,14} and levels are about 10% higher in men than in women of the same age.¹¹ This difference diminishes post-menopause.

Epidemiological and retrospective studies

In 1969, McCully¹⁵ was the first to suggest that elevated levels of Hcy might be associated with atherosclerosis. He based his theory on the fact that while the estimated prevalence of hyper-Hcy in the general population is between five and seven per cent, it approaches 30% in patients with coronary artery disease (CAD) and ranges between 55% and 85% in cardiac transplant patients.¹⁵

Two big meta-analysis studies^{16,17} supported the "homocyst(e)ine theory of atherosclerosis," suggesting a strong, dose-dependent, positive association between plasma-Hcy level and risk for CVD, which is independent of other known risk factors. Boushey¹⁶ concluded that 10% of the total population's CAD risk appears attributable to total homocysteine (tHcy) levels.

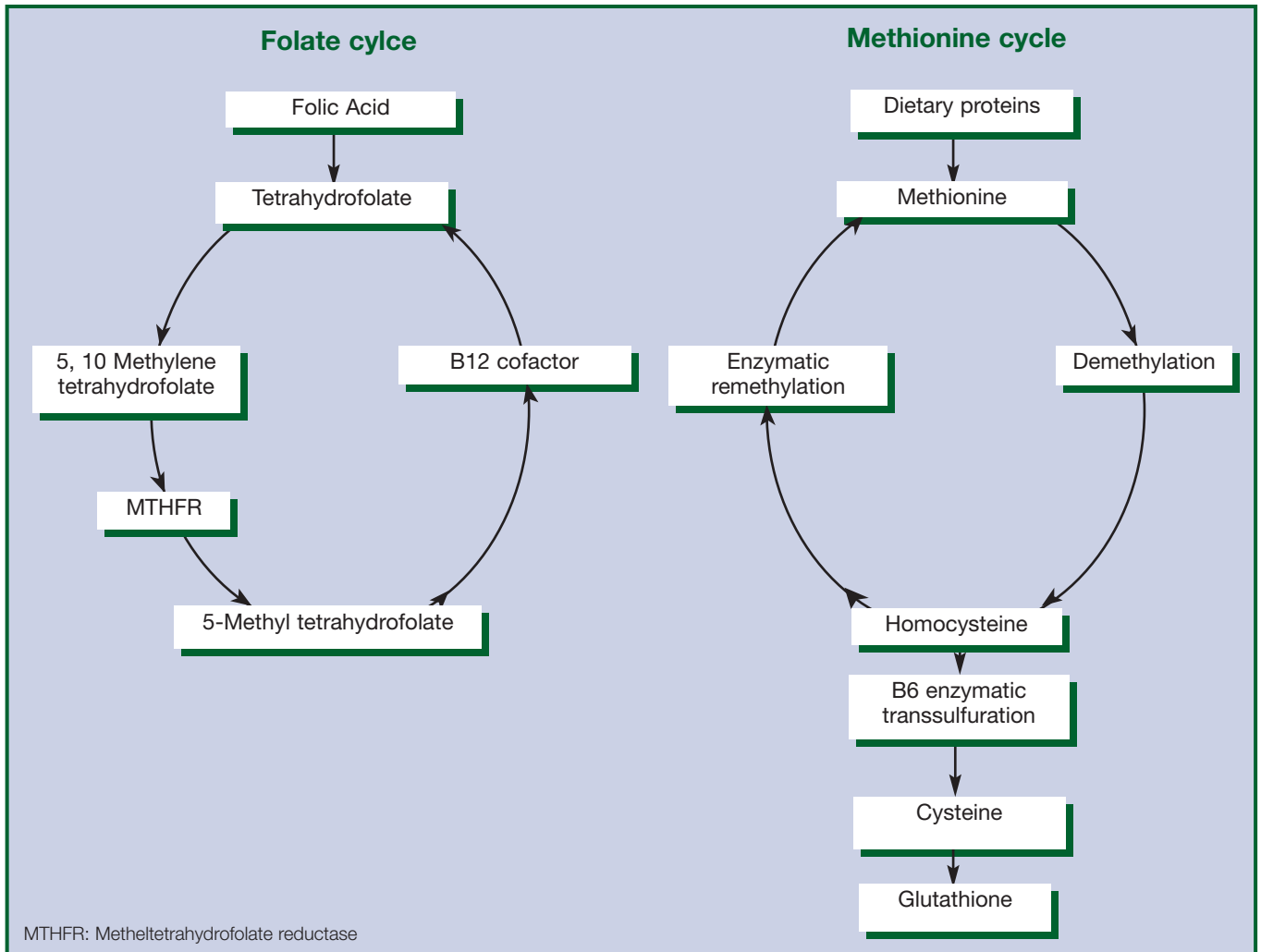


Figure 1. Simplified scheme of the homocysteine cycle.

Unfortunately, these two meta-analyses relied mostly on data from epidemiologic, cross-sectional and case-controlled studies, while data from the prospective studies were less consistent. As a result, Eikelboom¹⁷ raised some doubts and concluded that epidemiologic observations of an association between Hcy and CV risk do not confirm the existence of a causal relation.

The Homocysteine Lowering Trialists' Collaboration, in 1998¹² and 2002,¹⁸ were able to show that supplementation with folic acid (0.5 mg to five milligrams daily) reduced

blood-Hcy levels by 25%, while the addition of vitamin B12 (0.5 mg daily) produced an additional seven per cent reduction. Supplementation with vitamin B6 (16.5 mg daily) had no significant effect on Hcy levels.¹⁸

Most recent prospective studies

Several large prospective RCT's were recently published.¹⁹⁻²¹ They tried to determine whether lowering blood-Hcy concentrations reduces the risk of CVD in high-risk populations with established CVD.

In the 2004 Vitamin Intervention for Stroke Prevention (VISP) trial,¹⁹ Toole failed to determine whether best medical and surgical management, risk factor modification and a multivitamin (containing high-dose folic acid, vitamin B6 and B12) would reduce the incidence of recurrent cerebral infarction. The study also looked into coronary heart disease (CHD) and death in patients with a non-disabling cerebral infarction (and fasting tHcy levels greater than the 25th percentile for stroke patients).

The authors followed 3,680 post-stroke patients for an average of two years. Their primary end points were:

- ischemic stroke,
- CHD events and
- death.

The treatment, which successfully decreased the Hcy levels, had no effect on the outcome measures of stroke, CHD events, or death. Baseline tHcy was found to be an independent predictor of the outcomes.

The Norwegian Vitamin (NORVIT) trial,²¹ published in 2006, examined the potential benefit of vitamin B therapy in 3,749 patients with an acute MI. Patients were followed for five years. Their primary end points were:

- recurrent MI,
- stroke and
- sudden death attributed to CAD.

As expected, folic acid, plus vitamin B12 (but not B6 alone), lowered the mean tHcy level by 27%. As in the Vitamin Intervention for Stroke Prevention study,¹⁹ neither treatment with folic acid and B12 (with or without vitamin B6), was associated with a significant benefit in the end points.

Hcy-lowering vitamins are not currently indicated for the prevention of CVD.

There was an unexpected trend toward an increased risk (RR = 1.22) of the total number of end points in the group treated with all three vitamins. This combination therapy was associated with a 30% increased risk of non-fatal MI. Vitamin B6 therapy alone was associated with a 17% increased risk of MI. The baseline level of tHcy was shown to be statistically significant as a predictor of the primary end-point; however, after the adjustment for the creatinine level, it became non-significant.

The authors suggested that such treatment may promote atherothrombosis, affect endothelial function and

support cell growth through mechanisms that are independent of Hcy.

The authors concluded that high-dose vitamin B therapy should not be prescribed for the secondary prevention of CVD.

In the HOPE-TOO trial,²¹ the largest study, published in 2006, Lonn and her colleagues were confronted with the same question of whether prolonged administration of folic acid, combined with vitamins B6 and B12, reduces the risk of major vascular events in persons at high CV risk. They followed 5,522 patients with either vascular disease or diabetes, plus one other risk factor for an average of five years. As with the previous two studies, they were able to demonstrate that even though the baseline-Hcy level was a statistically significant predictor of CV events and regardless of the fact that the combination therapy successfully decreased its level, there were no significant difference in the rates of death from CVD and MI.

Chronic medical disorders and medical problems	<ul style="list-style-type: none"> • Renal failure • Hyperproliferative disorders • Hypothyroidism • Rheumatoid arthritis • Acute-phase response to illness • Cardiac and renal transplant patients 	<ul style="list-style-type: none"> • Malignant neoplasms & leukemia • Severe psoriasis • Diabetes • Systemic lupus erythamatosus
Drugs	<ul style="list-style-type: none"> • Some anticonvulsant agents (phenytoin, carbamazepine) • Cholesterol-lowering agents (cholestyramine, colestipol, nicotinic acid) • Folate antagonists (methotrexate) • Vitamin B12 antagonists (nitrous oxide) • Vitamin B6 antagonists, • Sex hormones • L-DOPA • Isoniazid • Metformin • Thiazide diuretics • Cyclosporine, <i>etc.</i> 	
Lifestyle factors	<ul style="list-style-type: none"> • Tobacco use • Alcohol and coffee intake • Emotional stress 	<ul style="list-style-type: none"> • Physical inactivity • Obesity
Enzyme deficiencies and mutations (genetics)	<ul style="list-style-type: none"> • Cystathionine b-synthase • Methylenetetrahydrofolate reductase • Cobalamin mutations, <i>etc.</i> 	<ul style="list-style-type: none"> • Methionine synthase
Vitamin deficiencies	<ul style="list-style-type: none"> • Folate • Increased methionine consumption 	<ul style="list-style-type: none"> • Vitamin B6 • Vitamin B12
Demographic	<ul style="list-style-type: none"> • Increasing age • Postmenopausal women 	<ul style="list-style-type: none"> • Male gender
Incorrect sample handling	<ul style="list-style-type: none"> • Unchilled blood 	

There was a 24% reduction of ischemic stroke in those assigned to the combination treatment group (RR = 0.7) without any distinction between different baseline Hcy levels.

On the other hand, more people were hospitalized for unstable angina in the combined treatment group (RR = 1.04), without any other differences in heart failure, or revascularization. The authors do not support the use of folic acid and B vitamin supplements as a preventive treatment since the combined intake of Hcy-lowering vitamins had no beneficial effects on major vascular events in high-risk populations with CVD.


Conclusions regarding B-vitamins

Although the baseline levels of tHcy are shown to be a statistically significant predictor of CVD in high-risk populations, its decrease does not improve the outcomes. Furthermore, it might promote atherosclerosis and increase the risk of MI and unstable angina.

Is this a paradox? Not necessarily. Some researchers^{22,24} suggest that Hcy might only be a marker for increased risk of CHD and not a cause, or that the combined treatment is harmful. Either way, Hcy-lowering vitamins are not currently indicated for the prevention of CVD.

Conclusion

No clinical benefits and sometimes even harmful effects were observed in a recent prospective RCT aiming to prevent CV events with vitamin E or Hcy-lowering vitamins.

Regardless of the explanations, there is no indication for prescribing vitamins E, folic acid, B12 or B6 for the prevention of CVD. 

References:

- Verlangieri AJ, Bush MJ: Effects of d-alpha-tocopherol supplementation on experimentally induced primate atherosclerosis. *J Am Coll Nutr* 1992; 11(2):131-8.
- Mehta J: Intake of antioxidants among American cardiologists. *Am J Cardiol* 1997; 79(11):1558-60.
- The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342(3):154-60.
- Lonn E, Bosch J, Yusuf S, et al: Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. *JAMA* 2005; 293(11):1338-47.
- Lee IM, Cook NR, Gaziano JM, et al: Vitamin E in the primary prevention of cardiovascular disease and cancer: The Women's Health Study: A randomized controlled trial. *JAMA* 2005; 294(1):56-65.
- Vivekananthan DP, Penn MS, Sapp SK, et al: Use of antioxidant vitamins for the prevention of cardiovascular disease: Meta-analysis of randomized trials. *Lancet* 2003; 361(9374):2017-23.
- Eidelman RS, Hollar D, Hebert PR, et al: Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease. *Arch Intern Med* 2004; 164(14):1552-6.
- Miller ER III, Pastor-Barriuso R, Dalal D, et al: Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; 142(1):37-46.
- Kris-Etherton PM, Lichtenstein AH, Howard BV, et al: Antioxidant vitamin supplements and cardiovascular disease. *Circulation* 2004; 110(5):637-41.
- Mosca L, Appel LJ, Benjamin EJ, et al: Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004; 109(5):672-93.
- Clarke R, Lewington S: Homocysteine and coronary heart disease. *Semin Vasc Med* 2002; 2(4):391-9.
- Lowering blood homocysteine with folic acid based supplements: Meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. *BMJ* 1998; 316(7135):894-8.
- Gauthier GM, Keevil JG, McBride PE: The association of homocysteine and coronary artery disease. *Clin Cardiol*. 2003; 26(12):563-8.
- Jacobsen DW: Practical chemistry of homocysteine and other thiols. In: Carmel R, Jacobsen DW (eds). *Homocysteine in Health and Disease*. Cambridge University Press, Cambridge, 2001, pp. 9–20.
- McCully KS: Vascular pathology of homocysteinemia: Implications for the pathogenesis of arteriosclerosis. *Am J Pathol* 1969; 56(1):111-28.
- Boushey CJ, Beresford SA, Omenn GS, et al: A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 1995; 274(13):1049-57.
- Eikelboom JW, Lonn E, Genest J Jr, et al: Homocyst(e)ine and cardiovascular disease: A critical review of the epidemiologic evidence. *Ann Intern Med* 1999; 131(5):363-75.
- Homocysteine and risk of ischemic heart disease and stroke: A meta-analysis. The Homocysteine Studies Collaboration. *JAMA* 2002; 288(16):2015-22.
- Toole JF, Malinow MR, Chambless LE, et al: Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction and death: The vitamin intervention for stroke prevention (VISP) randomized controlled trial. *JAMA* 2004; 291(5):565-75.
- Bonaa KH, Njolstad I, Ueland PM, et al: Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006; 354(15):1578-88.
- Lonn E, Yusuf S, Arnold MJ, et al: Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006; 354(15):1567-77.
- Spence JD: Homocysteine: Call Off the Funeral. *Stroke* 2006; 37(2):282-283.
- Loscalzo J: Homocysteine trials--clear outcomes for complex reasons. *N Engl J Med* 2006; 354(15):1629-32.