Homocysteine — Folate or Folic Acid and B Vitamins Are No Longer Recommended for Cardiovascular Risk Reduction

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Homocysteine has long been recognized as an abnormality that is elevated in some patients with vascular diseases such as stroke or heart attack or venous clots. Treatment with B vitamins, especially folate, can be used to lower the level of the chemical homocysteine found in blood.

Many physicians have recommended that the homocysteine level be checked as part of a multi marker strategy to assess the risk for vascular disease. Evaluation of homocysteine in addition to cholesterol levels and glucose levels and hs-CRP can help define a patient’s overall risk. By defining the risk in patients, more intense treatments can be used for higher risk patients and lower risk patients can receive less treatments. The rationale for treatment of elevated homocysteine with folate has been recommended for several years by many cardiologists because:

- Folate definitely lowers the level of homocysteine and higher levels correlate with a greater risk of vascular disease
- Folate is inexpensive and available without a prescription
- Folate is a water-soluble vitamin and vitamin supplementation is felt to be safe, although megadoses can cause irreversible peripheral neuropathy
- Many patients prefer a natural or non-pharmaceutical approach to prevention
- Cardiovascular diseases such as stroke and heart attack causes significant disability and death for patients so physicians and patients are often highly motivated to reduce risk

Because of these reasons many physicians, including me, have recommended a vitamin supplementation approach. This strategy has changed thanks to important new clinical trial date. In the New England Journal of Medicine, in April 2006, 2 large clinical trials were published which investigated this topic.

The trials title and summaries are:

**Homocysteine lowering and cardiovascular events after acute myocardial infarction**

BACKGROUND: Homocysteine is a risk factor for cardiovascular disease. We evaluated the efficacy of homocysteine-lowering treatment with B vitamins for secondary prevention in patients who had had an acute myocardial infarction. METHODS: The trial included 3749 men and women who had had an acute myocardial infarction within seven days before randomization. Patients were randomly assigned, in a two-by-two factorial design, to receive one of the following four daily treatments: 0.8 mg of folic acid, 0.4 mg of vitamin B12, and 40 mg of vitamin B6; 0.8 mg of folic acid and 0.4 mg of vitamin B12; 40 mg of vitamin B6; or placebo. The primary end point during a median follow-up of 40 months was a composite of recurrent myocardial infarction, stroke, and sudden death attributed to coronary artery disease. RESULTS: The mean total homocysteine level was lowered by 27% among patients given folic acid plus
vitamin B12, but such treatment had no significant effect on the primary end point (risk ratio, 1.08; 95% confidence interval, 0.93 to 1.25; P=0.31). Also, treatment with vitamin B6 was not associated with any significant benefit with regard to the primary end point (relative risk of the primary end point, 1.14; 95% confidence interval, 0.98 to 1.32; P=0.09). In the group given folic acid, vitamin B12, and vitamin B6, there was a trend toward an increased risk (relative risk, 1.22; 95% confidence interval, 1.00 to 1.50; P=0.05). CONCLUSIONS: Treatment with B vitamins did not lower the risk of recurrent cardiovascular disease after acute myocardial infarction. A harmful effect from combined B vitamin treatment was suggested. Such treatment should therefore not be recommended.

Homocysteine lowering with folic acid and B vitamins in vascular disease.

BACKGROUND: In observational studies, lower homocysteine levels are associated with lower rates of coronary heart disease and stroke. Folic acid and vitamins B6 and B12 lower homocysteine levels. We assessed whether supplementation reduced the risk of major cardiovascular events in patients with vascular disease. METHODS: We randomly assigned 5522 patients 55 years of age or older who had vascular disease or diabetes to daily treatment either with the combination of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12 or with placebo for an average of five years. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, and stroke. RESULTS: Mean plasma homocysteine levels decreased by 2.4 micromol per liter (0.3 mg per liter) in the active-treatment group and increased by 0.8 micromol per liter (0.1 mg per liter) in the placebo group. Primary outcome events occurred in 519 patients (18.8%) assigned to active therapy and 547 (19.8%) assigned to placebo (relative risk, 0.95; 95% confidence interval, 0.84 to 1.07; P=0.41). As compared with placebo, active treatment did not significantly decrease the risk of death from cardiovascular causes (relative risk, 0.96; 95% confidence interval, 0.81 to 1.13), myocardial infarction (relative risk, 0.98; 95% confidence interval, 0.85 to 1.14), or any of the secondary outcomes. Fewer patients assigned to active treatment than to placebo had a stroke (relative risk, 0.75; 95% confidence interval, 0.59 to 0.97). More patients in the active-treatment group were hospitalized for unstable angina (relative risk, 1.24; 95% confidence interval, 1.04 to 1.49). CONCLUSIONS: Supplements combining folic acid and vitamins B6 and B12 did not reduce the risk of major cardiovascular events in patients with vascular disease.

In the USA, the FDA is often criticized for taking a conservative and cautious approach to allowing claims of benefit from drug manufacturers. In 1999, the FDA evaluated data for and against the claim that B vitamins were of benefit. Evidence showed that folic acid and, to a lesser extent, cyanocobalamin and pyridoxine, did lower homocysteine. Yet, at that time, there were insufficient data to prove any link between elevated homocysteine levels and increased risk of vascular disease. The agency was therefore unwilling to allow any claims about B vitamins and cardiovascular risk in 1999. Shortly thereafter, the FDA initiated a new review of over 35 more recent studies. Suggestive (not conclusive) evidence indicated that elevated homocysteine levels are associated with the risk of vascular disease, based on prospective, case-control, and cross-sectional research. This research did not answer whether some other unidentified variable affects both and thus could not conclusively confirm whether lowering homocysteine would reduce the risk of vascular disease.
Due to the limitations of existing data, the FDA allowed a qualified health claim for folic acid, pyridoxine, and cyanocobalamine: "It is known that diets low in saturated fat and cholesterol may reduce the risk of heart disease. The scientific evidence about whether folic acid, vitamin B6 and vitamin B12 may also reduce the risk of heart disease and other vascular diseases is suggestive, but not conclusive. Clearly the FDA’s cautious position has been vindicated and this lesson is useful for patients and physicians alike as we consider other therapies in the future.

The point of these two studies for patients and clinicians goes beyond the specific findings of the lack of benefit from these “logical strategies”. These two trials of over 9000 patients not only failed to demonstrate a benefit but suggest harm from the use of these vitamins. This data adds to our knowledge that another vitamin strategy Vitamin E is not effective and is probably harmful for cardiovascular event reduction. The “take home” message is that patients and clinicians should be cautious about all health strategies regardless of how sensible or logical or safe it may appear until it has been assessed in a well conducted clinical trial that can be reviewed by health care professionals and shared with patients.