Meta-analysis shows no heart benefits for folic acid supplements

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Use of folic acid supplements appears to lower blood levels of the amino acid homocysteine-theorized to be a risk factor for heart and blood vessel disease-but does not appear to be associated with reduced rates of cardiovascular events, cancer or death over a five-year period, according to a meta-analysis of previously published studies in the October 11 issue of *Archives of Internal Medicine*.

"Elevated plasma total homocysteine [an amino acid created by the body, usually as a byproduct of eating meat] has been suggested as a potentially modifiable risk factor for coronary heart disease, stroke and other occlusive vascular conditions," the authors write as background information in the article. High rates of cardiovascular disease in children with homocystinuria-a rare genetic condition causing extreme elevations in homocysteine levels-led researchers to hypothesize that moderate increases in blood homocysteine levels may increase cardiovascular disease risk in the general population.

Supplementation with B vitamins, and in particular folic acid, lowers blood homocysteine levels and reduces cardiovascular disease risk among individuals with homocystinuria. Several large clinical trials conducted in patients without the condition have been inconclusive. "Consequently, a collaboration between their investigators was established in 2004 to conduct a meta-analysis based on individual participant data from all large randomized trials of folic acid - based B-vitamin supplementation intended to lower plasma homocysteine levels for the prevention of cardiovascular disease," the authors write.

Robert Clarke, F.R.C.P., University of Oxford, England, and colleagues in the B-Vitamin Treatment Trialists' Collaboration report the results of the meta-analysis of all eight trials completed by the end of 2009. Of a total of 37,485 participants, 18,723 were assigned to take folic acid in doses ranging from 0.8 milligrams per day to 40 milligrams per day. The other 18,762 took placebo or an equivalently small dose of folic acid. Trials continued for a median (midpoint) of five years.

Among the 37,485 participants, 9,326 had a major vascular event during the treatment period, 3,010 developed cancer and 5,125 died. Overall, there was a 25 percent reduction in homocysteine levels associated with active folic acid supplementation. However, those who took folic acid were no less likely to have a major heart or blood vessel event than those who took placebo (4,670 or 24.9 percent of first events occurred in those taking folic acid, compared with 4,656 or 24.8 percent in the placebo group).

In addition, there was no significant difference between folic acid and placebo groups in the number of patients experiencing major coronary events (2,019 or 11.4 percent vs. 1,971 or 11.1 percent); stroke (747 or 4.2 percent vs. 781 or 4.4 percent); new cases of cancer (1,541 or 8.7 percent vs. 1,469 or 8.2 percent) or death (2,578 or 13.8 percent vs. 2.547 or 13.6 percent).

"The doses of folic acid used in all the trials included in this meta-analysis exceeded those required for near-maximal reduction in homocysteine levels," the authors write. "The randomized trials in the present meta-analysis found no evidence of benefit with treatment continued for more than five years. Although some benefit might emerge with even longer treatment and follow-up, the trial results give no reason to expect this (particularly because cardiovascular benefits tend to emerge within just a few years with other cardioprotective treatments, such as antihypertensives or statins)."

"One-third of adults in the United States and one-quarter of those in the United Kingdom report taking daily multivitamin supplements containing folic acid," they conclude. All doses in the trials were greater than those required in the United States, where foods are fortified with folic acid to prevent neural tube birth defects. "Although the lack of any other benefits is disappointing (albeit fairly definitive), the lack of any significant adverse effects on vascular events, cancer incidence, cancer mortality and overall mortality provides reassurance about the safety of population-wide folic acid fortification."

More information: *Arch Intern Med.* 2010;170[18]:1622-1630.

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