

## Is folic acid the answer?<sup>1,2</sup>

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In 1969 McCully proposed his “homocysteine theory of arteriosclerosis,” ie, that elevated homocysteine concentrations may be a cause of cardiovascular disease (CVD) in the general population (1). The first evidence was reported in 1976, when Wilcken and Wilcken showed a relation between abnormal homocysteine metabolism and coronary artery disease (CAD) (2). Since then, the results of numerous studies have led to the conclusion that the association between total homocysteine (tHcy) and CVD is strong, graded, and independent of the conventional risk factors (3). However, the association seems to be largely confined to populations already at high risk of CVD events (4).

Because folate concentrations are an important determinant of tHcy, it is surprising that reports on the relation between folate status and CVD have been slow to catch up. A seminal study in 1996, the Nutrition Canada Survey (5), reported that low serum folate concentrations are associated with an increased risk of fatal CAD events. Other studies have followed, and the overall impression is that there is a modest inverse relation between serum folate concentrations and CVD risk (3).

In this issue of the Journal, Voutilainen et al (6) report their data from the Kuopio Ischaemic Heart Disease Risk Factor Study, a population-based study of 810 men aged 46–64 y who had no previous history of CAD. Acute coronary events were observed in 61 of the men during a follow-up of 7.7 y. Compared with the men with serum folate concentrations in the lowest tertile, those with concentrations in the highest tertile had an adjusted relative risk of acute coronary events of 0.35 (95% CI: 0.17, 0.73). In contrast, there was no association between tHcy and the risk of acute coronary events (relative risk: 1.03; 95% CI: 0.57, 1.87).

This new report extends the same authors' findings in 2 previous reports. One was a report of a nested case-control study of the same population in which the baseline was in 1984 and the follow-up was in 1996: tHcy concentrations were almost identical in 163 cases and 163 controls (11.24 compared with 11.20  $\mu\text{mol/L}$ , respectively). Logistic regression showed no evidence that elevated tHcy was a risk factor for CAD (7). In the second of their earlier reports (8), the same baseline (ie, 1991–1993) was used as in the new report, but the follow-up time was 5.3 y, and the number of cases with events was only 34. In that earlier study, mean serum folate concentrations in the cases and controls were 9.4 and 10.5  $\text{nmol/L}$ , respectively (ie, identical to the concentrations reported in the new study). The value of this new study lies in the longer follow-up time with more cases and in the fact that both folate and tHcy concentrations were measured in the same baseline samples and in the entire cohort.

The most surprising finding in this Finnish male population is that low folate concentrations are associated with increased risk of CAD events independently of tHcy concentrations. Most other studies have found that the effect of low folate concentrations is mediated at least in part by tHcy (3). The other main finding, ie, that elevated tHcy is not a risk factor in a population in whom subjects with prior CAD were excluded, is less surprising. In 2002 the Homocysteine Studies Collaboration reported the result of a large meta-analysis, which included a total of 5073 CAD events and 1113 stroke events. They concluded that tHcy is at most a modest CVD risk factor in the general population (9). This finding may be used as an argument against the homocysteine theory. In my opinion, the finding only shows that in a population with a low overall risk of CVD and in whom most subjects have normal tHcy concentrations, tHcy is not a strong risk factor. Indeed, even in high-risk populations (ie, patients with CVD, renal failure, diabetes, etc), for whom tHcy is a consistently strong risk factor, the marked increase in risk is predominantly observed in those with a tHcy concentration  $>15 \mu\text{mol/L}$  (4). Unfortunately, the Homocysteine Studies Collaboration did not report the risk in subjects with a tHcy concentration  $>15 \mu\text{mol/L}$ . Nevertheless, the findings from the meta-analysis, as well as those from the Kuopio Ischaemic Heart Disease Risk Factor Study, suggest that homocysteine may be overrated as a potential causal risk factor for CVD.

Supplementation with B vitamins, particularly including folic acid, reduces tHcy concentrations. However, whether such treatment prevents CVD events is unknown; this can be determined only by large-scale clinical trials. Unfortunately, current trials cannot distinguish between the risk due to elevated tHcy and that due to low folate status. Nearly all the trials include high doses of folic acid, which influence folate concentrations as well as tHcy concentrations, and most of the trials also include high doses of vitamin B-12 or vitamin B-6 (3). What are missing are trials using agents such as betaine that lower tHcy independently of folate.

Some reports from trials using folic acid and vitamins B-12 and B-6 in combination are now available. In healthy siblings of patients with atherosclerotic disease, B vitamins decreased the occurrence of abnormal results on an exercise electrocardiography test but did not improve peripheral arterial abnormalities (10). In renal transplant recipients, the intima-media thickness of

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carotid arteries decreased 32% in those who were treated with B vitamins but increased 23% in those who received placebo (11). B vitamins may also reduce restenosis after percutaneous transluminal coronary angioplasty, but predominantly in vessels without stents (12).

The Vitamin Intervention for Stroke Prevention (VISP) trial is the largest published study to date on this topic and the only one to report hard endpoints. In this trial, which compared a high-dose B vitamin formulation (2.5 mg folic acid, 5 mg vitamin B-6, 0.4 mg vitamin B-12) with a low-dose formulation (20  $\mu$ g folic acid, 200  $\mu$ g vitamin B-6, 6  $\mu$ g vitamin B-12), the incidence of stroke or CVD events did not differ between the 2 treatment groups (13). The result may seem disappointing. However, most of the participants were recruited in the United States and Canada after folic acid fortification had begun. Moreover, both groups were treated with the low-dose formulation during the 1-mo run-in period, ie, before the baseline sample. The vitamin B-12 content in the low-dose formulation was 2.5 times the recommended dietary allowance and is sufficient to normalize vitamin B-12 status in most subjects. Thus, with this design and in a population eating folic acid-fortified food, it is not surprising that there was only a 15% difference in tHcy concentrations between the 2 groups. Such a small difference would be expected to have a limited effect on stroke events. However, not even a trend was observed, which suggests that B vitamins and homocysteine are not important for the development of stroke events.

The results from the VISP trial appear to be in stark contrast with preliminary data from the Centers for Disease Control and Prevention, which suggest that folic acid fortification has had a striking effect on mortality, particularly on stroke mortality (Internet: <http://www.medicalnewstoday.com/index.php?newsid=6369>). The reduction in tHcy concentrations after fortification was 14%, ie, similar to that achieved in the VISP trial, but the increase in serum folate concentrations was only from 15 to 34 nmol/L, compared with an increase from  $\approx$ 30 to  $\approx$ 80 nmol/L in the VISP trial. Is it possible that fortification with low-dose folic acid is better than the high-dose multivitamin combinations used in the VISP trial and in most other ongoing trials? In contrast, could the lack of effect in the VISP trial be due to a ceiling effect in relation to folate status?

What shall we do? Is folic acid fortification the answer? Fortification has reduced the prevalence of neural tube defects, but for every infant saved, several hundred thousand Americans are now eating fortified food (14). The data from the Kuopio Ischaemic Heart Disease Risk Factor Study and from the Centers for Disease Control and Prevention support the view that increased folate intake could have a positive effect on our health. Data from other sources, including the VISP trial and the Homocysteine Studies Collaboration, however, suggest that one should not jump to conclusions. The fact is that the evidence is conflicting

and, except for neural tube defects, the beneficial effect of improved folate status remains to be established.

More than ever we need to be patient and wait for the results from ongoing trials. Additional trials are needed to provide the evidence for other conditions in which tHcy or folate has been implicated, including pregnancy complications, cancer, and cognitive decline in the elderly (4, 15). Health authorities want simple answers at low cost. Folic acid is inexpensive, is probably safe, and could be very effective. We can only hope that public authorities recognize their obligations to fund research and trials that will reveal the correct public health measures for some of the most common diseases of mankind. 

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