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PREVENTION

B vitamins and CVD—failure to find a simple solution

Marta Ebbing and Per Magne Ueland

The hope that a simple, affordable, and safe homocysteine-lowering intervention with folic acid and vitamin B_{12} would improve outcomes for patients with established cardiovascular or renal disease has been crushed by the null results from large B-vitamin treatment trials completed to date.

The idea that an elevated circulating level of the sulfur-containing amino acid homocysteine is involved in the development of vascular occlusive disease was first proposed in 1969. The 'homocysteine theory' was brought forward by Kilmer McCully, who showed that similar vascular lesions were found in two patients with different inborn errors that were both associated with high levels of homocysteine.[1] McCully hypothesized that such lesions could be prevented with medical or dietary interventions aimed at lowering homocysteine level.[1] Since the early 1990s, this theory has been substantiated by experimental data suggesting that an increased level of homocysteine might cause vascular lesions.[1] In addition, case–control and prospective cohort studies have demonstrated that circulating levels of homocysteine are associated with the incidence and prognosis of coronary artery disease and stroke.[1] In a meta-analysis of cohort studies conducted in healthy populations, Humphrey *et al.* concluded that, for each 5 μmol/l increment in plasma total homocysteine level, the risk of coronary events increases by 18% independently of traditional risk factors for coronary artery disease.[2] However, the results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH),[3] now published in the *Journal of the American Medical Association*, demonstrate that administration of homocysteine-lowering B vitamins has no beneficial effects on cardiovascular health.

Oral administration of folic acid (the synthetic form of folate), alone or in combination with vitamin B_{12}, lowers homocysteine level.[1] In SEARCH,[3] 12,064 patients with a history of myocardial infarction were randomly assigned to receive 2 mg of folic acid plus 1 mg of vitamin B_{12}, or placebo, to assess whether lowering homocysteine levels would be associated with a reduction in the incidence of major adverse cardiovascular events (MACEs; defined as coronary death, myocardial infarction, and stroke) or revascularization. The average duration of intervention was 6.7 years.[3] This study is the largest of the homocysteine-lowering trials conducted to date,[4] and was powered to detect a 10% reduced risk of the primary end point with the B-vitamin treatment at a 5% significance level. The lack of benefit from B vitamins observed in SEARCH[3] is disappointing, but is in line with the results of the other large homocysteine-lowering secondary-prevention trials conducted among patients with established cardiovascular or renal disease.[4] The positive message from SEARCH[3] was that the vitamin treatment was not associated with an increased risk of cancer, which has previously been suggested.[5,6]

Folic acid has been the cornerstone treatment in homocysteine-lowering B-vitamin trials, and has been given in doses ranging from 0.8 mg per day to 40 mg per day.[4] These doses far exceed the recommended dietary allowances of 0.4 mg per day. Although folate status is a major determinant of circulating homocysteine level, vitamins B_{12}, B_2, and B_6, and one-carbon donors such as choline and betaine are also involved in regulating homocysteine level.[1,7] The complexity of these interactions has been summarized in the concept of a 'B-vitamin cross-talking network', which implies that the effect of one component on homocysteine depends on the levels of the others.[7] In terms of healthy nutrition, the interactions between B vitamins in humans remind us that these micronutrients are not present at high doses of a single vitamer in natural food, but rather at balanced and physiological levels of multiple B vitamins.[8]

An elevated circulating level of homocysteine is also associated with a variety of factors that do not primarily reflect B-vitamin status, including several risk factors for cardiovascular disease, such as smoking, low physical activity, high blood pressure, high total-cholesterol levels and impaired renal function.[9] Notably, among patients with ischemic heart disease participating in two Norwegian homocysteine-lowering trials, baseline plasma homocysteine level was not an independent predictor of cardiovascular events. However, homocysteine level, measured after 1–2 months of intervention with folic acid and vitamin B_{12}, was a significant predictor of subsequent MACEs.[10] This finding could indicate that the fraction of plasma homocysteine not responsive to treatment with B vitamins is linked to cardiovascular disease progression.

There are several possible explanations why treatment with homocysteine-lowering B vitamins did not prevent cardiovascular events in SEARCH,[3] or in other secondary-prevention trials with hard clinical end points.[4] First, an elevated level of homocysteine could be an epiphenomenon related to processes involved in the development of vascular lesions and might not itself have a causal role. Second, short-term (up to 7 years) treatment with B vitamins might not reverse or stop the progression of vascular occlusion in individuals with established disease. This idea does not, however, preclude a protective effect of long-term intervention in healthy individuals. Third, high doses of single vitamins, or a combination of just a few vitamins, might not affect putative

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homocysteine compartment(s)—that is, the cells or pathways in which homocysteine is involved—that affect vascular lesions or functions, or could even have adverse effects that offset the possible benefits of lowering homocysteine levels.

> “...agents that more-specifically modify ... homocysteine metabolism are theoretically attractive...”

So, what are the take-home messages from the null effects observed in SEARCH[3] and other secondary-prevention trials[4] with B vitamins in patients with cardiovascular disease? To investigate whether B vitamins have a primary preventive effect would require a sample size of tens of thousands of healthy individuals not exposed to folic acid through fortified foods, and an intervention period lasting for decades. Considering the substantial resources required, however, such trials are unlikely to be implemented. Secondary-prevention trials with agents that more-specifically modify certain aspects of homocysteine metabolism are theoretically attractive,[1] whereas additional trials with B vitamins are not justified. To further evaluate possible disease-modifying or clinical effects of B vitamins, the strategy should involve investigation of short-term and long-term effects of the interventions in trials already completed or underway. When results from all 11 trials in the B-Vitamin Treatment Trialists' Collaboration are available, new meta-analyses including individual data from more than 52,000 participants will be performed.[4] Finally, high doses of folic acid and vitamin B_{12} should not be recommended as preventive measures for patients with established cardiovascular or renal disease. The advice given to patients to improve their cardiovascular health should still be to avoid smoking and obesity, start exercising, have a healthy balanced diet with fruit and vegetables, and to control hypertension, hypercholesterolemia, and diabetes mellitus.

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Competing interests
P. M. Ueland declares an association with the following company: Bevital. See the article online for full details of the relationships. M. Ebbing declares no competing interests.

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HYPERTENSION

BP reduction in patients with diabetes—uncertainties remain

Michael A. Weber

Patients with diabetes mellitus and hypertension are at high cardiovascular risk and treatment guidelines recommend aggressive blood pressure (BP) control. However, a reanalysis of data from the previously published INVEST trial indicates that achieving systolic BPs <130 mmHg in patients with diabetes and coronary artery disease increases mortality, although this finding might reflect the speculative conclusions produced by post-hoc analyses.

Aggressively reducing blood pressure (BP) to <130/80 mmHg has been widely recommended for the prevention of cardiovascular events in patients with diabetes mellitus.[1,2] The results of studies published in the past year, however, have cast doubt on the value of this strategy.[3,4] One of these studies in particular—a retrospective analysis of data from the International Verapamil SR–Trandolapril Study (INVEST)[4]—has even raised the possibility that this BP target could be linked to adverse clinical outcomes. The authors of this paper reported that, among hypertensive individuals with diabetes and coronary artery disease enrolled in INVEST, achieving systolic BPs <140 mmHg produced clear cardiovascular benefits when compared with higher BPs; but, surprisingly, systolic BPs <130 mmHg were associated with significantly increased mortality ($P = 0.04$).[4] Even so, post-hoc analyses have well-established uncertainties, and the apparently straightforward conclusions of INVEST[4]—that reducing systolic BP to <140 mmHg is beneficial, but to <130 mmHg is dangerous—could risk violating Einstein's dictum that “everything should be made as simple as possible, but no simpler”.

The original INVEST randomized controlled trial[5] was designed to compare the outcome effects of BP-lowering treatment with either the β-blocker atenolol, or the calcium-channel blocker verapamil, in patients with hypertension and documented coronary artery disease. The principal results, published in 2003, indicated no major differences in clinical end points between the two regimens.[6] The current report by Cooper-DeHoff *et al.* focused on the 6,400 patients in the INVEST population who also had diabetes.[4] Investigators were advised that patients with diabetes should additionally receive the angiotensin-converting-enzyme inhibitor trandolapril as part of their initial

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