Efficacy of B Vitamins in Lowering Homocysteine in Older Men
Maximal Effects for Those With B₁₂ Deficiency and Hyperhomocysteinemia

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Background and Purpose—A higher plasma concentration of total homocysteine (tHcy) is associated with a greater risk of cardiovascular events. Previous studies, largely in younger individuals, have shown that B vitamins lowered tHcy by substantial amounts and that this effect is greater in people with higher tHcy and lower folate levels.

Methods—We undertook a 2-year, double-blind, placebo-controlled, randomized trial in 299 men aged ≥75 years, comparing treatment with a daily tablet containing 2 mg of folate, 25 mg of B₆, and 400 μg of B₁₂ or placebo. The study groups were balanced regarding age (mean±SD, 78.9±2.8 years), B vitamins, and tHcy at baseline.

Results—Among the 13% with B₁₂ deficiency, the difference in mean changes in treatment and control groups for tHcy was 6.74 μmol/L (95% CI, 3.94 to 9.55 μmol/L) compared with 2.88 μmol/L (95% CI, 0.07 to 5.69 μmol/L) for all others. Among the 20% with hyperhomocysteinemia, the difference between mean changes in treatment and control groups for men with high plasma tHcy compared with the rest of the group was 2.8 μmol/L (95% CI, 0.6 to 4.9 μmol/L). Baseline vitamin B₁₂, serum folate, and tHcy were significantly associated with changes in plasma tHcy at follow-up (r=0.252, r=0.522, and r=−0.903, respectively; P=0.003, <0.001, and <0.001, respectively) in the vitamin group.

Conclusions—The tHcy-lowering effect of B vitamins was maximal in those who had low B₁₂ or high tHcy levels. Community-dwelling older men, who are likely to be deficient in B₁₂ or have hyperhomocysteinemia, may be most likely to benefit from treatment with B vitamins. (Stroke. 2006;37:547-549.)

Key Words: aged ■ clinical trial ■ homocysteine ■ vitamins ■ vitamin B₁₂ deficiency
Results

Patients in the placebo and vitamin supplement group were evenly matched for age, B vitamin, and tHcy status at baseline (Table). Allocation to B-vitamin supplementation was associated with a significant increase at 6-month follow-up in mean blood concentrations of folate (10.6 nmol/L; 95% CI, 8.8 to 12.4) and vitamin B12 (258 pmol/L; 95% CI, 228 to 288) and a significant reduction in mean tHcy (3.9 μmol/L; 95% CI, 3.1 to 4.6; Table).

The effect of B-vitamin supplementation on tHcy was augmented among the 38 men (13%) with vitamin B12 deficiency (serum B12 <140 pmol/L) and the 65 men (20%) with hyperhomocysteinaemia (tHcy >15 μmol/L). B-vitamin supplementation reduced mean tHcy by 6.74 μmol/L (95% CI, 3.94 to 9.55 μmol/L) in men with vitamin B12 deficiency (Table). The difference in tHcy between mean changes in treatment and control groups for men with low serum B12 compared with the rest of the group was 2.88 μmol/L (95% CI, 0.07 to 5.69 μmol/L). Using a more liberal definition of relative B12 deficiency of <258 pmol/L, 152 men (55%) were found to be deficient. In comparison to the more severely B12-deficient men, the increase in serum B12 on treatment, when compared with placebo, was greater at 230.8 pmol/L (95% CI, 196.1 to 265.4 pmol/L), but the decrease in tHcy was less at 4.23 μmol/L (95% CI, 3.14 to 5.32 μmol/L).

Among men with hyperhomocysteinaemia, B-vitamin supplementation reduced mean tHcy by 6.63 μmol/L (95% CI, 4.61 to 8.65 μmol/L; Table). The difference between mean changes in treatment and control groups for men with high plasma tHcy compared with the rest of the group was 2.8 μmol/L (95% CI, 0.6 to 4.9 μmol/L). Only 3 men had a serum folate level below the lower limit of the reference range of 5.5 nmol/L. For those 29 men who had a serum folate in the lowest decile (<13.5 nmol/L), the effect of B-vitamin administration was augmented, with a difference of 6.91 μmol/L (95% CI, 4.05 to 9.77 μmol/L) in tHcy between the 2 groups. In the 150 patients assigned B-vitamin supplements, baseline vitamin B12, serum folate, and tHcy were significantly associated with changes in the concentration of plasma tHcy at follow-up (r=0.25, r=0.52, and r=-0.90, respectively; P=0.003, <0.0001, and <0.0001, respectively).

Discussion

These results support the findings of the metaanalysis from the Homocysteine Lowering Trialists’ Collaboration that the effect of B-vitamin therapy is more pronounced in people with higher tHcy and lower folate concentrations before treatment. In addition, our data indicate that, in an older
population with a high prevalence of vitamin B₁₂ deficiency, the effect of B-vitamin therapy was more pronounced in people with lower B₁₂ concentrations before treatment. If ongoing randomized trials show that lowering tHcy does reduce serious vascular events, community-dwelling older men, who are likely to be deficient in B₁₂ and at high absolute risk of vascular events and dementia, may be most likely to benefit.

**Summary**

Previous studies, largely in younger individuals, have shown that B vitamins lower plasma homocysteine by substantial amounts and that this effect is greater in people with higher homocysteine and lower folate levels. This study confirms this finding in older men, but shows, for the first time, that the homocysteine-lowering effect was maximal in those who had lower B₁₂ levels.

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