Efficacy of B Vitamins in Lowering Homocysteine in Older Men
Maximal Effects for Those With B$_{12}$ 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 $\geq$75 years, comparing treatment with a daily tablet containing 2 mg of folate, 25 mg of B$_6$, and 400 $\mu$g of B$_{12}$ or placebo. The study groups were balanced regarding age (mean $\pm$ SD, 78.9 $\pm$ 2.8 years), B vitamins, and tHcy at baseline.

Results—Among the 13% with B$_{12}$ deficiency, the difference in mean changes in treatment and control groups for tHcy was 6.74 $\mu$mol/L (95% CI, 3.94 to 9.55 $\mu$mol/L) compared with 2.88 $\mu$mol/L (95% CI, 0.07 to 5.69 $\mu$mol/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 $\mu$mol/L (95% CI, 0.6 to 4.9 $\mu$mol/L). Baseline vitamin B$_{12}$, 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 B$_{12}$ or high tHcy levels. Community-dwelling older men, who are likely to be deficient in B$_{12}$ 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 B$_{12}$ deficiency

High total plasma homocysteine (tHcy) is associated with increased risk of cardiovascular events and dementia. Recent evidence suggests that this association may be causal. A metaanalysis of 12 clinical trials involving 1114 individuals showed that between 0.5 and 5 mg of folic acid daily lowers tHcy by 25% (95% CI, 23% to 28%), with vitamin B$_{12}$ supplementation (0.02 to 1 mg daily) further reducing tHcy by 7%. The effect of B-vitamin therapy was more pronounced in people with higher tHcy and lower folate concentrations before treatment. However, the subjects included in this metaanalysis had a mean age of 52 years, most had normal folate and vitamin B$_{12}$ status, and the mean duration of B-vitamin treatment was only 6 weeks. Because vitamin B$_{12}$ deficiency is heavily age dependent, it is uncertain how effective sustained homocysteine-lowering therapy would be in later life. There is some evidence that, in patients with vascular disease, low B$_{12}$ levels are not only associated with elevated tHcy but also with carotid plaque area. Because recent published data suggest that, in the presence of folate repletion, blood concentrations of tHcy are highly dependent on vitamin B$_{12}$ status, we hypothesized that the effects of B-vitamin therapy in lowering tHcy may be augmented in populations with a high prevalence of B$_{12}$ deficiency.

Methods
We undertook a double-blind, placebo-controlled, randomized trial of homocysteine-lowering therapy in 299 elderly men aged $\geq$75 years, drawn from a population-based trial of screening for abdominal aortic aneurysm. These men were randomized to treatment with a tablet containing 2 mg of folate plus 25 mg of B$_6$ and 400 $\mu$g of B$_{12}$ or placebo to be taken once daily with breakfast for 2 years. Measurement of fasting plasma tHcy, serum B$_{12}$, and folate levels occurred at 6-monthly intervals. Details of recruitment and follow-up are outlined in the Figure. Informed consent was obtained from all of the subjects, and all of the study procedures were approved by the University of Western Australia Institutional Ethics Committee.
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 mol/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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