Homocysteine-lowering therapy did not prevent stroke recurrence

Toole JF, Malinow MR, Chambless LE, et al. **Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial.** JAMA. 2004; 291:565-75.

QUESTION

In patients with nondisabling cerebral infarction, do high doses of a homocysteine-lowering regimen of pyridoxine, cobalamin, and folic acid prevent stroke recurrence better than low doses of this regimen?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, patients, outcome assessors, {data collectors, data analysts, data safety and monitoring committee, and executive committee}†),* placebo-controlled trial with mean 20-month follow-up (Vitamin Intervention for Stroke Prevention [VISP]).

SETTING

56 clinical centers in the United States, Canada, and Scotland.

PATIENTS

3680 patients who were ≥ 35 years of age (mean age 66 y, 63% men) and had nondisabling ischemic stroke and elevated total homocysteine (tHcy) levels. Exclusion criteria included embolic stroke, other major neurologic illness, life expectancy < 2 years, need for dialysis, and untreated anemia or vitamin B_{12} deficiency. Follow-up was 92%.

INTERVENTION

Patients were allocated to high (n = 1827) or low (n = 1853) doses of homocysteine-lowering therapy. The high-dose group received a daily multivitamin tablet that included pyridoxine, 25 mg; cobalamin, 0.4 mg; and folic acid, 2.5 mg. The low-dose group received a daily multivitamin tablet that included pyridoxine, 200 µg; cobalamin, 6 µg; and folic acid, 20 µg. All patients received the best available medical and surgical management to prevent recurrent stroke (i.e., risk factor control education and aspirin, 325 mg/d).

MAIN OUTCOMES

Recurrent ischemic stroke and coronary heart disease (CHD) events (myocardial infarction [MI] requiring hospitalization, coronary revascularization, cardiac resuscitation, and fatal CHD).

MAIN RESULTS

Analysis was by intention to treat. The high- and low-dose groups did not differ for recurrent ischemic stroke, CHD, or death (Table). The study had 80% power to detect a 30% difference in stroke between the high-dose and the low-dose groups.

CONCLUSION

In patients with nondisabling cerebral infarction, a multivitamin tablet with high doses of pyridoxine, cobalamin, and folic acid did not differ from a low-dose tablet for reducing recurrent stroke.

Source of funding: National Institute of Neurological Disorders and Stroke.

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*See Glossary.
†Information provided by author.

High-dose pyridoxine, cobalamin, and folic acid vs low-dose pyridoxine, cobalamin, and folic acid in cerebral infarction at 2 years‡

Outcomes	High dose	Low dose	RRI (95% CI)	NNH
Recurrent ischemic stroke	9.2%	8.8%	0% (–20 to 30)	Not significant
			RRR (CI)	NNT
Coronary heart disease	7.0%	7.4%	10% (–20 to 30)	Not significant
Death	5.9%	6.9%	10% (–10 to 30)	Not significant

‡Abbreviations defined in Glossary; event rates, RRI, RRR, NNH, and NNT based on Kaplan-Meier analysis.

COMMENTARY

Elevated tHcy is associated with atherogenesis and thrombosis and with an increased risk for ischemic stroke independent of other vascular risk factors; this association is strong, dose-related, and biologically plausible. However, randomized controlled trials (RCTs) have not shown that lowering tHcy (via folic-acid–based multivitamin therapy) reduces stroke.

The VISP trial is the first large RCT evaluating the effect of folic-acid–based multivitamin therapy on such "hard" clinical outcomes as stroke. It did not identify a significant benefit of high-dose, compared with low-dose, therapy. However, it did not reliably exclude a modest but important reduction in the relative risk for stroke of ≤ 20%, and perhaps even greater risk reductions with greater reductions in tHcy. The (unexpectedly) small difference in tHcy between the high- and low-dose groups may reflect the widespread vitamin supplement use and fortification of grains and staple foods with folate in North America. Greater reductions may be achieved in other populations where food is not supplemented with folate.

Because the VISP trial has not proven multivitamin therapy to be effective or ineffective in preventing serious vascular events among patients with previous stroke, more data are needed to refine the estimates of effectiveness and to provide placebo-controlled estimates of effectiveness in other populations with different prevalences of genetic and environmental factors that influence tHcy. The VITAmins TO Prevent Stroke (VITATOPS) trial has randomized > 4000 patients with recent ischemic stroke from 19 countries in 4 continents to placebo or folic acid, 2 mg; vitamin B_{12}, 0.5 mg; and vitamin B_6, 25 mg, and aims to randomize 8000 patients (http://vitatops.highway1.com.au) (1).

While awaiting the results of ongoing trials of folic-acid–based multivitamin therapy in other patient groups (2), insufficient evidence exists to recommend routine screening and treatment of high tHcy with folic acid and other vitamins to prevent atherothrombotic vascular disease.

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References

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