Homocysteine-lowering therapy did not prevent stroke recurrence


**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 B₁₂ 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.

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*See Glossary.
†Information provided by author.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>High dose</th>
<th>Low dose</th>
<th>RRI (95% CI)</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent ischemic stroke</td>
<td>9.2%</td>
<td>8.8%</td>
<td>0% (−20 to 30)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>7.0%</td>
<td>7.4%</td>
<td>10% (−20 to 30)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Death</td>
<td>5.9%</td>
<td>6.9%</td>
<td>10% (−10 to 30)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

†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 recurrent 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.

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.

**References**