Vitamin B in Stroke Prevention: a journey from Observational studies to RCT's.

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The Role of Vitamin B in Stroke Prevention

A Journey From Observational Studies to Clinical Trials and Critique of the VITAmins TO Prevent Stroke (VITATOPS)

Gustavo Saposnik, MD, MSc, FAHA

All truths are easy to understand once they are discovered; the point is to discover them.
—Galileo Galilei (1564 to 1642), Italian physicist, astronomer, and philosopher

The role of vitamins in stroke prevention has been studied for decades. Folate and cyanocobalamin (vitamin B12) are important regulators of the metabolism of homocysteine. Studies have shown that low levels of these factors are associated with elevation of homocysteine in the blood. Hyperhomocysteinemia has been associated with premature atherosclerosis with an increased risk of cardiovascular events. On the basis of epidemiological studies, clinicians and scientists expected that homocysteine-lowering therapy (HLT) with appropriate doses of folic acid, Vitamin B6, and Vitamin B12 supplementation would reduce the incident risk of cardiovascular diseases (including stroke). As a result, HLT has been tested in several double-blind, randomized controlled trials (Table 1).

I discuss the results of the recently published VITAmins TO Prevent Stroke (VITATOPS) trial in the context of the current available evidence. Needless to say, this article is not a comprehensive review, but rather it intends to highlight some of the current and relevant aspects of Vitamin B supplementation for stroke prevention. As such, several questions will remain to be answered.

The VITATOPS Trial

VITATOPS was a double-blind, placebo-controlled trial, in which 8164 patients with a recent stroke or transient ischemic attack were randomized to receive placebo or 2 mg folic acid, 25 mg vitamin B6, and 0.5 mg Vitamin B12 in a single tablet. Follow-up ranged to nearly 12 years with a median of 3.5 years. The qualifying events were ischemic (88%), hemorrhagic (10%), and unknown (2%). Of the ischemic events, large artery disease was the most common stroke mechanism, and approximately one third of patients had small vessel disease. Patients were ethnically diverse: 42% white, 24% Asian, 26% southern Asian, and 7% other. The primary outcome was nonfatal stroke, nonfatal myocardial infarction, or vascular death. Among participants, 616 (15%) patients assigned to B vitamins and 678 (17%) assigned to placebo reached the primary end point (risk ratio [RR] 0.91; 95% CI, 0.82 to 1.00; P=0.05; absolute risk reduction, 1.56%; −0.01 to 3.16). No significant benefit was observed for stroke reduction (RR, 0.92; 0.81 to 1.06). There were no serious adverse reactions and no significant differences in common adverse effects between the treatment groups. Neither adherence to medication nor follow-up was different between groups. Complete follow-up was available in 91% of patients.

The Good and the Bad

VITATOPS was an investigator-driven trial over a period of 12 years. The investigators are to be commended for their efforts in conducting this large trial over 12 years but, importantly, for obtaining funding to study an inexpensive product (B vitamins), which is commercially available and would be unlikely to generate a substantial revenue per pill for any sponsor. Unfortunately, the results of the VITATOPS do not provide sufficient evidence to support B vitamin supplementation for secondary stroke prevention. Rather, it adds more controversy to the current debate.

What Do We Not Know?

As mentioned, Vitamin B therapy has been associated with homocysteine reduction, also called HLT. Epidemiological studies and clinical trials showed that a 20% to 25% relative reduction in homocysteine levels (which correlated with 2.5 to 3 μmol/L absolute reduction) is associated with a significant reduction in cardiovascular events. Further reductions are less likely to be effective. Data from the reanalysis of the Vitamin Intervention for Stroke Prevention (VISP) and Heart Outcomes Prevention Evaluation (HOPE) 2 studies showed a graded effect in homocysteine reduction and clinical outcomes. Unfortunately, homocysteine levels in
VITATOPS were not available for most of patients as per financial limitations. Therefore, the published results based on the effect of Vitamin B therapy in the overall studied population provide limited estimation of the “real effect” once the target homocysteine reduction is achieved. The marginal benefits in favor of Vitamin B therapy were also eventually diluted by the use of lower doses of Vitamin B12 (0.5 mg). Elderly individuals require higher doses of B12 such as 1000 μg/day to achieve adequate absorption. Spence has discussed the key role of metabolic B12 deficiency, the interpretation of clinical trials, and the differences between myocardial infarction and stroke. He emphasizes that strokes are much more likely to be embolic, but thrombosis is more important in stroke pathogenesis. Elevated homocysteine quadruples the risk of stroke in atrial fibrillation. The role of homocysteine and HLT in different stroke subtypes (e.g., cardioembolic; large artery atherosclerotic disease, etc) has not been established.

### Kidney Function: A Marker or Confounder?

Some studies showed Vitamin B therapy may be harmful in patients with an underlying nephropathy. For example, in the DIVINe trial (Diabetic Intervention with Vitamins to Improve Nephropathy), 238 participants who had Type 1 or 2 diabetes and a clinical diagnosis of diabetic nephropathy were randomized to a single tablet of B vitamins containing folic acid (2.5 mg/day), Vitamin B6 (25 mg/day), and Vitamin B12 (1 mg/day) or matching placebo. For the primary outcome, radionuclide glomerular filtration rate (primary outcome) decreased by a mean (SE) of 16.5 (1.7) mL/min/1.73 m² in the Vitamin B group compared with 10.7 (1.7) mL/min/1.73 m² in the placebo group (mean difference, −5.8; 95% CI, −10.6 to −1.1; P = 0.02) at 36 months. There was a mean 2.2 μmol/L reduction in the homocysteine level in the Vitamin B group and a mean 2.6 μmol/L increase in the placebo group. Perhaps more importantly, there was a doubling of cardiovascular events with Vitamin B therapy that was confined to the patients with glomerular filtration rate <50 mL/min/1.73 m².

In another randomized trial including 2056 participants with advanced chronic kidney disease (estimated creatinine clearance ≥30 mL/min; n = 1305) or end-stage renal disease (n = 751) and high homocysteine levels (≥15 μmol/L), high doses of B vitamins (40 mg of folic acid, 100 mg Vitamin B6, and 2 mg Vitamin B12) showed no reduction in death, myocardial infarction, or stroke over placebo.

In VITATOPS, there was a significant reduction for the primary outcome among patients with normal creatinine levels (<120 mmol/L; RR, 0.83; 95% CI, 0.72 to 0.96) but not for their counterparts (creatinine >120 mmol/L; RR, 0.89; 95% CI, 0.65 to 1.21). Data should be interpreted with caution as for the nonsignificant probability value for the interaction (P = 0.80).

Together, these data merit some considerations: (1) Vitamin B therapy may be harmful in patients with impaired renal function; (2) the “true” effect of Vitamin B therapy in previous randomized trials, including cardiovascular outcomes, might have been diluted by the inclusion of patients with reduced glomerular filtration rate; and (3) in patients with renal failure and stroke, the more active forms of cyanocobalamin and folic acid (methylcobalamin and tetrahydrofolate) may help decrease the hyperhomocysteinemia.

### What Have We Learned?

In a recent meta-analysis including 13 randomized controlled trials that enrolled 39 005 participants, the authors found a lower incident risk of stroke (RR, 0.83; 95% CI, 0.71 to 0.97; P = 0.02) for the combination of folic acid with Vitamins B6 and B12. No significant benefit was found for the use of single folic acid supplementation compared with controls.


Table 2. Summary of Meta-Analysis Reporting Stroke Outcomes

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>No. of Trials</th>
<th>Key Inclusion Criteria</th>
<th>Outcome</th>
<th>Total No. of Participants (Active/Control)</th>
<th>Active</th>
<th>Control</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al(^\text{16})</td>
<td>8</td>
<td>RCT with folic acid supplementation</td>
<td>Stroke was an end point</td>
<td>16 841</td>
<td>373</td>
<td>4.17</td>
<td>405</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More than 10 events</td>
<td></td>
<td>179</td>
<td>7.70</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration of the intervention &gt;6 months</td>
<td></td>
<td>172</td>
<td>3.46</td>
<td>196</td>
</tr>
<tr>
<td>Lee et al(^\text{25})</td>
<td>13</td>
<td>Folic acid supplementation with or without Vitamin B6 or B12</td>
<td>Any Stroke</td>
<td>39 005</td>
<td>784</td>
<td>3.84</td>
<td>791</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ischemic</td>
<td>10 050</td>
<td>337</td>
<td>4.04</td>
<td>349</td>
</tr>
<tr>
<td>Clarke et al(^\text{26})</td>
<td>8</td>
<td>Double-blind RCT</td>
<td>Relevant treatment arms differed only with respect to lower Hcy levels</td>
<td>37 485</td>
<td>747</td>
<td>4.2</td>
<td>781</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At least 1000 participants</td>
<td></td>
<td>439</td>
<td>2.3</td>
<td>460</td>
</tr>
<tr>
<td>Bazzano et al(^\text{27})</td>
<td>12</td>
<td>RCT</td>
<td>Folic acid supplementation with or without B12</td>
<td>16 958</td>
<td>352</td>
<td>4.74</td>
<td>370</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mei et al(^\text{28})</td>
<td>17</td>
<td>RCT</td>
<td>Folic acid supplementation with or without B12</td>
<td>39 107</td>
<td>749</td>
<td>4.19</td>
<td>764</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al(^\text{29})</td>
<td>14</td>
<td>RCT</td>
<td>Folic acid supplementation with or without B12</td>
<td>38 941</td>
<td>19 444/19 497</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

RCT indicates randomized controlled trial; Hcy, homocysteine; NR, not reported.

(RR, 0.93; 95% CI, 0.85 to 1.03).\(^\text{25}\) Formal testing did not reveal any substantial resulting heterogeneity or publication bias. In another recent meta-analysis including 8 randomized trials (with at least 1000 participants and follow-up data for a minimum of 1 year and appropriate doses of folic acid) involving 37 485 individuals during a median follow-up of 5 years, folic acid allocation had no significant effects on vascular outcomes with rate ratios (95% CIs) of 1.01 (0.97 to 1.05) for major vascular events, 1.03 (0.97 to 1.10) for major coronary events, and 0.96 (0.87 to 1.06) for stroke. Four of the included randomized controlled trials use no or low doses (0.4 mg) of Vitamin B12.\(^\text{26}\) Interestingly, the treatment reached the expected target because there was an overall 25% mean reduction in homocysteine levels in individuals in the vitamin group compared with those in the placebo group. Other meta-analysis showed similar results (Table 2).\(^\text{16,25–29}\)

With the exception of the HOPE 2 trial\(^\text{10}\) and reanalysis of VISP,\(^\text{17,18}\) the remaining randomized studies showed no significant benefit in the reduction of stroke.

Only 2 trials (VISP and VITATOPS) primarily randomized patients with previous stroke or transient ischemic attacks.\(^\text{15,17}\)

Previous meta-analysis using similar inclusion criteria reported a nonsignificant reduction in cardiovascular disease (RR, 0.95; 95% CI, 0.88 to 1.03), coronary heart disease (RR, 1.04; 95% CI, 0.92 to 1.17), or stroke (RR, 0.86; 95% CI, 0.71 to 1.04) for folic acid supplementation (in some combined with Vitamin B).\(^\text{27}\) Critically, other authors reported a significant 18% (RR, 0.82; 95% CI, 0.68 to 1.00) reduction in the risk of stroke by focusing on a subset (7 of the previous 12 randomized studies) and added a randomized trial from China.\(^\text{16,30}\) The benefit was greater in those trials with longer treatment duration (>36 months; RR, 0.71, 95% CI, 0.57 to 0.87), blood level reduction of homocysteine of >20% (RR, 0.77; 95% CI, 0.63 to 0.94; Table 2), and no history of stroke (RR, 0.75; 95% CI, 0.62 to 0.90).\(^\text{16}\) Critiques to some of these trials include the use of lower doses of multivitamins, short intervention, limited number of stroke patients/events, and lack of complete homocysteine measures.\(^\text{31}\)

How Many More Clinical Trials and Meta-Analyses Do We Need to Determine the Role of Vitamin B Therapy in Stroke Prevention?

There are already several observational and randomized trials of HLT reporting on the risk of myocardial infarction and stroke. Interestingly, 4 meta-analyses reporting on the benefit of folic acid or Vitamin B supplementation were just published in 2010 (Table 2).\(^\text{25,26,28,29}\) Concordant observational data from cohort studies with over 10 years prospective follow-up showed that a
25% lower homocysteine level (approximately 3 μmol/L [0.41 mg/L]) was associated with an 11% (OR, 0.89; 95% CI, 0.83 to 0.96) lower ischemic heart disease and 19% (OR, 0.81; 95% CI, 0.69 to 0.95) lower stroke risk. Some meta-analyses have confirmed this finding. However, the overall results of randomized clinical trials (the recently reported Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine [SEARCH], Western Norway B Vitamin Intervention Trial [WENBIT], Women’s Antioxidant and Folic Acid Cardiovascular Study [WAFACS], Supplementation with FOLate, vitamin B6 and B12 and/or OMega-3 fatty acids [SU.FOL.OM3], VITATOPS, and the previously reported Linxian Nutrition Intervention Trial [LNIS], Atherosclerosis and Folic Acid Supplementation Trial [ASFAST], Homocystinemia in Kidney and End Stage Renal Disease [HOST], VISP, Norwegian Vitamin Trial [NORVIT], HOPE 2, and most recent meta-analyses25-29 of folic acid supplementation in vascular prevention (composite outcome) showed consistent negative results.

The association of vitamin deficiency and higher incident risk of a medical condition in observational studies with lack of risk reduction in randomized clinical trials is not new in medicine. Similar findings were observed for in studies analyzing the antioxidants properties of Vitamin C, Vitamin E, and beta-carotene.34-36

How About Stroke?
Together the reanalysis of the VISP trial and HOPE 2 trials is more encouraging. In HOPE 2, the benefit favoring HLT remained after adjusting for concomitant antithrombotics, lipid-lowering, and antihypertensive treatment at study entry (hazard ratio, 0.71; 95% CI, 0.56 to 0.91). Because both hypercholesterolemia and hyperhomocysteinemia can synergistically accelerate atherosclerosis in individuals at risk, treating both conditions may be a more effective intervention in stroke prevention. On the basis of the results of subgroup analysis from meta-analysis, only selected patients (ie, those with no history of stroke living in areas with no grain fortification or those with elevated baseline homocysteine levels capable of responding to HLT) may benefit with the long-term supplementation of appropriate doses of multivitamins (2.5 mg folic acid, 50 mg Vitamin B6, and 1 mg Vitamin B12) for stroke prevention.6

Another meta-analysis with more restricted criteria showed no benefit in stroke reduction even when there was an overall 25% mean reduction (target usually accepted as effective) in homocysteine levels.6

At the present time, the general or routine use of folic acid supplementation for cardiovascular prevention is not beneficial. The recent published Guidelines for the Primary Prevention of Stroke state that the use of the B-complex vitamins, pyridoxine (B6), cobalamin (B12), and folic acid might be considered for prevention of ischemic stroke in patients with hyperhomocysteinemia, but its effectiveness is not well established (Class Ib; Level of Evidence B). A similar level of recommendation is provided in the Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (Secondary prevention). Although possible, another trial powered to detect an absolute reduction in the risk of stroke with appropriate dose of vitamin supplements and long follow-up is unlikely to happen. The potential low-profit, likely marginal (if demonstrated) clinical effects of HLT and required efforts to conduct a large multicenter trial make this less attractive to sponsors.

Several questions remain to be answered regarding the benefit of Vitamin B complex therapy (or HLT) before (and after!) the results of the VITATOPS trial, meta-analyses, and this succinct review.

Take-Home Messages for Clinicians
(i) High homocysteine levels are associated with increased risk of both stroke and coronary heart disease.
(ii) Homocysteine can be lowered with folic acid (2.5 mg) and B-complex vitamin (50 mg B6 and 1 mg B12) supplements.
(iii) The routine use of HLT for cardiovascular prevention is not supported by the current available evidence.
(iv) Individuals with ischemic stroke and hyperhomocysteinemia may benefit from HLT for secondary prevention.
(v) Although Vitamin B complex does not appear to have major side effects, caution must be exercise in patients with renal failure or decreased glomerular filtration rate.

Acknowledgments
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