Folic Acid–Based Multivitamin Therapy to Prevent Stroke
The Jury Is Still Out

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here is a large body of observational and laboratory evidence suggesting but not proving that increasing plasma concentrations of total homocysteine (tHcy) is a causal risk factor for atherothromboembolic ischemic stroke and other vascular events.1–9

Recent publication of the results of the landmark Vitamins in Stroke Prevention (VISP) Trial is the first evidence from a large randomized controlled trial (RCT) of the effect of lowering tHcy via folic acid–based multiple B vitamin supplementation on the incidence of “hard” clinical events, such as recurrent stroke, in patients with recent ischemic stroke.10,11 In contrast to what was expected from the epidemiological evidence, the VISP Trial did not identify a significant treatment effect of lowering tHcy by vitamin therapy on recurrent stroke, coronary events, or death, despite confirming a consistent and graded association between baseline tHcy and vascular risk (particularly the probability of stroke over time).11 Recruiting primarily from North America, VISP enrolled 3680 recent (3 to 120 days) survivors of nondisabling, noncardiogenic, ischemic stroke with baseline tHcy above the 25th percentile of the North American stroke population into a double-blind, randomized comparison of high versus low doses of a combination of 12 different vitamins, including folic acid, vitamin B12, vitamin B6, and riboflavin, which are cofactors for enzymes responsible for metabolizing homocysteine.11 After 2 years of follow-up, there was no significant difference in the cumulative incidence of the primary outcome event of recurrent cerebral infarction: 8.4% of 1814 patients who were allocated to high-dose multivitamins [including 2.5 mg of folic acid, 0.4 mg of vitamin B12, and 25 mg of vitamin B6] versus 8.1% of 1835 patients allocated to low-dose multivitamins [including 0.02 mg of folic acid, 0.006 mg of vitamin B12, 0.2 mg of vitamin B6]; risk ratio [RR], 1.0; 95% CI, 0.8 to 1.3; P=0.80.11 There was a nonsignificant reduction in death (5.4% in the high-dose group versus 6.3% in the low-dose group; RR, 0.9, 95% CI, 0.7 to 1.1) and the combined outcome of any stroke, coronary heart disease, or death (16.7% in the high-dose group versus 17.2% in the low-dose group; RR, 1.0; 95% CI, 0.8 to 1.1).11

Is the Homocysteine Hypothesis of Atherothrombosis Still Viable?
The first issue the VISP Trial results may challenge is whether the “homocysteine hypothesis” of atherothrombotic vascular disease is valid and whether it is perhaps another example of “hype” generated by observational studies that have identified an association between a marker of risk (tHcy) and an increased incidence of vascular disease but have failed to adjust for residual confounding by unknown or unrecorded risk factors or markers of risk. Recent examples include reports from observational studies of significant associations between antioxidant nutrients and hormone replacement therapy and reduced vascular disease, which were later refuted by large RCTs of antioxidant and hormone replacement therapy, respectively.12,13

We believe the homocysteine hypothesis of atherothrombotic vascular disease in general, and stroke in particular, remains viable. Two recent studies using different methods yield consistent results in support of the hypothesis.9,14 In the Health Professional Follow-Up Study, the risk of ischemic stroke among 43 732 healthy men followed for 14 years was 29% (95% CI, 4% to 48%) lower among men whose dietary intake of folate was in the highest quintile compared with the lowest quintile.14 Although men with higher folate intake exercised more, were more likely to take aspirin regularly, and were less likely to be overweight or current smokers, the association was not altered substantially after adjustment for these more healthy lifestyle factors.14 It is possible that other unmeasured and unknown risk factors were not adjusted for in this study. However, these results and those of other observational studies1–9 are consistent with those of a “ran-
domized” trial of “nature.”

Among individuals with a mutation in the gene coding for methylene tetrahydrofolate reductase (MTHFR), in which cytosine is replaced by thymidine at base position 677 of the gene, affected individuals have reduced activity of the MTHFR gene, increased tHcy by \( \approx 20\% \), and an increased risk of stroke and other major vascular events.\(^8,9\) The presence or absence of this mutation in the MTHFR gene in any individual is an example of “random” assignment (by nature [ie, by genotype]) to a higher or lower tHcy. The results suggest that higher tHcy is associated with a higher risk of stroke and other vascular events, with a similar magnitude of association to that observed in other observational studies. Because the respective studies were prone to different potential sources of bias, it is compelling to still suggest that increased tHcy may be a causal risk factor for stroke.\(^9,14\)

**Are the VISP Trial Results a True or a False Negative?**

The second question is whether the results of VISP accurately reflect a true lack of effect of folic acid–based multivitamin therapy in preventing major vascular events (ie, a true negative) or whether they are a type-II error (ie, a false negative) resulting from lack of statistical power.

We believe that VISP did not have the statistical power to reliably exclude a modest but clinically important effect of folic acid–based multivitamin therapy in reducing the risk of major vascular events and death by up to 20% and 30%, respectively.

The VISP Trial was designed on the assumption that it would be possible to achieve and maintain a difference in tHcy between the high-dose and low-dose vitamin treatment groups of 4 to 6 \( \mu \text{mol/L} \), and hence, a reduction in the cumulative incidence of recurrent stroke during 2 years from 12% to 8.4% (relative risk reduction 30%).\(^10\) However, in practice, the achieved absolute difference in mean tHcy was only 2 \( \mu \text{mol/L} \) (13 \( \mu \text{mol/L} \) in patients allocated low-dose vitamins versus 11 \( \mu \text{mol/L} \) in patients allocated high-dose vitamins).\(^11\) The (unexpectedly) small difference of 2 \( \mu \text{mol/L} \) in tHcy is likely to reflect the high prevalence of vitamin supplement use in the North American community and the widespread fortification of the grain supply and staple foods in North America with folate that coincided with the inception of the VISP Trial.\(^11,15,16\) The latter may have reduced the statistical power of VISP by as much as 75%.\(^17\) Furthermore, the vitamin regimen used in VISP may have contained too little vitamin B\(_6\) in the high-dose group and too much in the low-dose group (more than the recommended daily intake) because in the presence of folate repletion, blood concentrations of tHcy are highly dependent on vitamin B\(_6\).\(^18\) The lower-than-anticipated rates of recurrent stroke in both treatment groups and the short duration of follow-up (2 years) also limited the statistical power of the VISP Trial. As the VISP investigators state, to confirm a statistically significant reduction in all-cause mortality of 10% (the size of the nonstatistically significant reduction observed in the VISP Trial), a sample size of 20,000 patients would have been required.\(^11\)

We believe this underlines the importance of rapid completion of the other ongoing trial of folic acid–based B multivi-

itamin therapy in patients with recent stroke, the VITAmins TO Prevent Stroke (VITATOPS) trial, which has presently recruited \( \geq 4000 \) patients from 70 centers in 19 countries of 5 continents, and aims to follow up \( \geq 8000 \) randomized patients for a mean of \( \geq 2.5 \) years.\(^19\)

The VITATOPS Trial has adopted a somewhat different approach to testing whether the homocysteine hypothesis can be translated into a useful therapeutic intervention (Table).\(^10,11,19\) It is recruiting from the full spectrum of survivors of recent transient ischemic attacks of the brain and eye and is well-powered and not applying any eligibility criterion regarding level or metabolism of homocysteine at baseline. Some of these patients have low baseline tHcy and are therefore likely to derive at best only a modest absolute benefit from homocysteine-lowering therapy. However, the sample size calculations are based on predicted frequencies of a cumulative end point of new stroke, myocardial infarction, or vascular death of 8% per year in the control group, which receives a placebo, and 6.4% in the group receiving the active combination of only 3 compounds: folic acid plus vitamin B\(_6\) plus vitamin B\(_12\).\(^19\) These more conservative predictions of relative risk reductions (a decrease of 15% in VITATOPS versus 30% in VISP) explain why VITATOPS needs to accrue at least double the number of primary outcome events as in VISP.

We have considered carefully whether VITATOPS should proceed now that VISP has returned an “equivocal” result and believe there are several reasons why VITATOPS should continue.

First, the lower extreme of the 95% CIs of the estimates of VISP for the major outcome events is consistent with high-dose multivitamin therapy, reducing the risk of recurrent ischemic stroke by \( \approx 20\% \) and death by \( \approx 30\% \).\(^11\) Perhaps even greater risk reductions can be achieved with greater reductions in tHcy, as may be achieved in other populations in which food is not supplemented with folate. These are clinically important treatment effects that cannot afford to be missed because of a type-II error. Indeed, several smaller recent trials of folic acid–based multivitamin therapy have reported similar and statistically significant benefits in surrogate measures of vascular events\(^20–24\) and a reduction in clinical events.\(^25,26\)

Second, the VISP Trial has not revealed any evidence of harm from attempts to reduce tHcy. Although the most recent clinical trial has suggested accelerated rates of restenosis in patients receiving folate and vitamin B\(_12\) and vitamin B\(_6\) supplements compared with placebo after coronary revascularization,\(^27\) the totality of evidence indicates continuing uncertainty as to benefit and harm from vitamin supplements and a lack of conclusive proof as to either.

Third, even if VISP had indicated significant benefits associated with vitamin use, it would still be important to complete VITATOPS as planned, as well as other large trials of homocysteine lowering in nonstroke patients\(^1\) because of the ever-present chance that a type-I error had occurred and the result was a “false positive.”

Finally, the VITATOPS Trial aims to complement the experience of VISP by refining precision of the estimates of vitamin therapy effects on preventing stroke and other major vascular events in the same type of patients included in VISP.
and VITATOPS, and to extend the experience of VISP by exploring the effect of vitamin therapy in a broader range of patients (eg, with all ranges of tHcy), countries (eg, in Europe, Asia, and Australasia), and outcomes (eg, dementia and depression), and over a longer period of follow-up, as well as compared with placebo (Table). The individual patient data will ultimately contribute to a systematic review by the Homocysteine Lowering Trialists Collaboration (Robert Clarke, Clinical Trials Service Unit, Oxford, UK).

**Implications for Researchers and Clinicians**

Currently, increased tHcy remains to be proven as a causal risk factor for ischemic stroke, and folic acid–based multivitamin therapy remains to be proven as a safe and effective (or ineffective) treatment to reduce the risk of stroke. Because there is consistent evidence of a possible causal association between tHcy and stroke risk from different epidemiological studies that are prone to different sources of bias, and because the VISP Trial has not reliably excluded a modest but clinically important effect of vitamin therapy, 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. While awaiting the results of ongoing trials of folic acid–based multivitamin therapy and meta-analyses of these trials, insufficient evidence exists to recommend routine screening and treatment of high tHcy with folic acid and other vitamins to prevent atherothrombotic vascular disease. However, some clinicians will undoubtedly continue this empirical practice in selected high-risk patients for whom the potential benefits are believed to outweigh the potential risks and costs.

**References**

3. Eikelboom JW, Hankey GJ, Anand SS, Loftiouse H, Staples N, Baker RI. Association between high homocysteine and ischaemic stroke due to...


