Unmasking the benefits of B vitamins in stroke prevention

Gustavo Saposnik
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Vitamin B₆ and folate are key mediators of homocysteine metabolism. Low plasma vitamin B₆ and folate concentrations are associated with hyperhomocysteinemia, with subsequent premature atherosclerosis and increased risk of cardiovascular and cerebrovascular disease. In a meta-analysis of observational studies, a 25% reduction in homocysteine concentrations (roughly 3 μmol/L [0·41 mg/L]) corresponded with an 11% lower risk of ischaemic heart disease and a 19% lower risk of stroke. The Heart Outcomes Prevention Evaluation 2 (HOPE 2) trial and re-analysis of data from the Vitamin Intervention for Stroke Prevention (VISP) study (both trials in which patients received high doses of B vitamins) have confirmed these findings for stroke. Conversely, the results of other randomised clinical trials, including the Vitamins to Prevent Stroke (VITATOPS) trial, of folate supplementation in prevention of vascular events (primary composite outcome) showed consistent negative results. One meta-analysis suggested a benefit of vitamin-B supplementation when it was given for a longer duration (>36 months), led to a greater than 20% reduction in homocysteine levels, and was used in patients with no history of stroke.

In this issue of The Lancet Neurology, Graeme Hankey and colleagues assessed whether antiplatelet treatment modifies the effect of B vitamins on stroke prevention in a post-hoc analysis of data from the VITATOPS trial. Of 8072 patients with previous stroke or transient ischaemic attack randomly assigned to receive one tablet daily of placebo or B vitamins (2 mg folic acid, 25 mg vitamin B₆, and 500 μg vitamin B₁₂) for whom antiplatelet therapy status was available, 6609 patients (81%) were taking antiplatelet drugs and 1463 (18%) were not. For antiplatelet users, B vitamins had no significant effect on the primary outcome (stroke, myocardial infarction, or vascular death). By contrast, B-vitamin supplementation in participants not taking antiplatelet drugs at baseline was associated with a 24% reduction in the primary outcome compared with placebo (16·8% vs 21·0%; hazard ratio [HR] 0·76, 95% CI 0·60–0·96). There was an interaction between antiplatelet treatment and supplementation with B vitamins (adjusted p for interaction=0·0204). Hankey and colleagues concluded that antiplatelet treatment modifies the potential benefits of homocysteine-lowering treatment (B vitamins) in the secondary prevention of major cardiovascular events.
In the VITATOPS trial, patients taking antiplatelet drugs were more likely to have large artery and small vessel disease. Conversely, nearly 50% of participants not taking antiplatelet drugs had a haemorrhagic stroke as the qualifying event.11 Participants not taking antiplatelet drugs were more likely to be younger, east Asian, and have history of hypertension or atrial fibrillation. These participants were less likely to be smokers, have dyslipidaemia, or have diabetes.11

The main findings from the VITATOPS trial showed no significant benefit of B-vitamin supplementation for stroke reduction.1 However, this subgroup analysis showed a 35% reduction in the risk of stroke (HR 0·65, 95% CI 0·46–0·91) and a 29% reduction in the primary composite outcome (0·71, 0·55–0·90) in patients not taking antiplatelet drugs, after adjustment for the effects of imbalances in baseline variables. There was a significant interaction for the association between antiplatelet exposure and B-vitamin supplementation.11 There was also a reduced risk of haemorrhagic stroke with B vitamins compared with placebo in participants not taking antiplatelet drugs (p for interaction=0·0757). No subtypes of stroke showed reduced risk with B vitamins versus placebo in both the antiplatelet treatment and no antiplatelet treatment groups.

The hypothesis that antiplatelet treatment modifies vitamin-B supplementation is not new. In a subgroup analysis of HOPE 2 trial, the incidence of stroke in participants not taking aspirin (about 20% of participants) was significantly lower in those randomly assigned to receive B-vitamin supplementation (4·8% vs 8·0%; HR 0·60, 95% CI 0·39–0·92).12 No benefit was noted in patients taking aspirin (3·7% vs 4·5%; 0·83, 0·61–1·13; unpublished). Nevertheless, caution was advised since there was no significant interaction (p=0·22) between aspirin and supplementation with B vitamins.13 A recent meta-analysis of randomised trials of homocysteine reduction on cardiovascular disease (cardiac death and non-fatal myocardial infarction) favoured vitamin-B supplementation in those studies with lower prevalence of antiplatelet use.14 Another study suggested a protective effect of plasma folate in patients with haemorrhagic stroke (but not ischaemic stroke), who are less likely to be on antiplatelet drugs,15 the large number of patients not taking antiplatelet drugs who had a haemorrhagic event might therefore help to explain the findings from VITATOPS.

As acknowledged by Hankey and colleagues, their exploratory subanalysis—which is therefore subject to potential bias or competing risk—might serve to generate a hypothesis rather than establish causality. Furthermore, the VITATOPS trial was not powered to establish the benefit of vitamin-B supplementation by stroke subtype (eg, cardioembolic, large artery disease, small vessel disease).6

In summary, this subgroup analysis, in view of the available evidence, suggests that the discordant results from observational studies and previous randomised trials could be explained by antiplatelet drugs attenuating or cancelling a small benefit of homocysteine-lowering therapy with B vitamins in cardiovascular prevention. The findings from the study also suggest that, in patients with raised homocysteine, vitamin-B supplementation might potentially have a role in primary stroke prevention (for non-antiplatelet users). However, vitamin-B supplementation does not seem to have a significant benefit in secondary prevention of stroke and cardiovascular disease when antiplatelet therapy is taken routinely. Although further studies might confirm these findings, it is unlikely this information would substantially change clinical practice in view of the wide (and currently recommended) use of antithrombotic drugs in secondary prevention of cardiovascular events and the challenges associated with designing and doing a clinical trial with a non-prescription and inexpensive intervention such as B vitamins.

Gustavo Saposnik
Stroke Outcomes Research Unit, Stroke Outcomes Research Canada, Division of Neurology, Department of Medicine, St Michael’s Hospital, and Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada; and Institute for Clinical Evaluative Sciences and Li Ka Shing Knowledge Institute, Toronto, ON, Canada saposnikg@smh.ca

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Errata

Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al, for the PREDICT/Sunnybrook ICH CTA study group. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. Lancet Neurol 2012; 11: 307-14—In this Article (published online March 8), on page 307 in the Abstract, and on page 310 in the Results, it was stated that the positive predictive value for the CT-angiography spot sign was 73%, the negative predictive value was 84%, with 63% sensitivity and 90% specificity. These statements were incorrect and should have read 61% (95% CI 47-73) for the positive predictive value and 78% (73-84) for the negative predictive value, with 51% (39-63) sensitivity and 85% (78-90) specificity. This correction has been made to the online version as of May 16, 2012.

Walter S, Kostopoulou P, Hazz A, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. Lancet Neurol 2012; 11: 397-404—In the Summary (p 397) and the Methods (p 400) the ClinicalTrials.org number should have been NCT00732220. This correction has been made to the online version as of May 16, 2012.