Differential Effect of B-Vitamin Therapy by Antiplatelet Use on Risk of Recurrent Vascular Events After Stroke

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Background and Purpose—Although several randomized controlled trials failed to show a benefit of B vitamin therapy on composite outcomes of cardiovascular death, myocardial infarction, and stroke among individuals with elevated homocysteine, recent post hoc analyses have suggested that several factors may interact with the effects of vitamin treatment. One post hoc analysis revealed an interaction between B vitamin therapy and antiplatelet use; however, those results have not been replicated in other studies or populations.

Methods—We conducted a post hoc analysis of the Vitamin Intervention for Stroke Prevention (VISP) trial, a randomized controlled trial evaluating treatment with high- versus low-dose B vitamin therapy for secondary prevention of vascular events among stroke survivors with elevated homocysteine. Cox regression models were used to assess primary (recurrent stroke) and secondary (stroke, myocardial infarction, or vascular death) outcomes among individuals on high- versus low-dose vitamin therapy, categorized by antiplatelet use, after adjusting for covariates.

Results—Among 3680 participants, 52% took antiplatelet medications. When compared with low-dose therapy, high-dose vitamin therapy was associated with higher stroke risk among individuals on antiplatelets (hazard ratio, 1.43; 95% confidence interval, 1.02–2.01), but trended toward lower risk among those not on antiplatelets (hazard ratio, 0.86; 95% confidence interval, 0.62–1.19).

Conclusions—High-dose B vitamin therapy may be associated with a higher risk of recurrent stroke among stroke survivors taking antiplatelets, but does not have a significant effect on recurrent stroke risk in those who are not on antiplatelets. Future randomized controlled trials may consider evaluating the effect of homocysteine lowering among stroke survivors with elevated homocysteine who are not on antiplatelet therapy. (Stroke. 2015;46:870-873. DOI: 10.1161/STROKEAHA.114.006927.)

Key Words: antiplatelet agents ■ homocysteine ■ myocardial infarction ■ stroke ■ vitamin B complex

Although homocysteine is a known independent vascular risk factor,1 numerous large randomized controlled trials (RCTs) have failed to show that treating elevated homocysteine lowers composite outcomes of cardiovascular death, myocardial infarction (MI), and stroke among stroke survivors.2–5 Although many factors may be responsible for the lack of benefit in these large RCTs, a major factor may be the widespread fortification of grains with folic acid in countries where the RCTs were conducted. Fortification of grains in 1996 lowered baseline average homocysteine levels from 10.1 to 9.4 μmol/L in the United States.6 Perhaps the benefit of homocysteine lowering is only seen among individuals with significant elevations in serum homocysteine. In addition, recent post hoc analyses of RCTs and observational data have suggested interactions between vitamin therapy and several factors, including B12 levels, renal function, and age. Indeed, vitamin supplementation with higher doses of B12, exclusion of patients with chronic kidney disease, and inclusion of only younger stroke survivors may show that homocysteine lowering is beneficial.7–11 A recent post hoc subgroup analysis of the VITAMinS TO Prevent Stroke (VITATOPS) trial12 revealed that antiplatelet therapy modifies the potential benefits of lowering homocysteine.12 In the subgroup of patients not taking antiplatelet medications, B vitamin supplementation lowered the rate of stroke, MI, and death from vascular causes.13 These results have not been replicated in other studies. Our aim was to assess the interaction between antiplatelet use and B vitamins for lowering homocysteine in individuals with recent stroke who participated in the Vitamin Intervention for Stroke Prevention (VISP) Trial.

Methods and Design

Patient Population

The VISP trial was a multicenter, double-blind RCT performed at centers across the United States (n=45), Canada (n=10), and Scotland (n=1) designed to determine whether best medical therapy and a multivitamin containing high-dose folic acid, pyridoxine, and cobalamin...
given to lower total homocysteine levels would reduce the incidence of recurrent cerebral infarction in patients with a nondisabling ischemic stroke versus low-dose vitamin therapy. The study design has been described in detail previously. Briefly, demographic, clinical, and laboratory data were collected at baseline, with subsequent clinical and laboratory information obtained at follow-up visits 6, 12, 18, and 24 months. Participants were enrolled after undergoing written informed consents. The trial was approved by the ethics committee at each participating center. The primary outcome was recurrent stroke and secondary outcome was stroke, MI, or death from a vascular cause.

Statistical Analysis
Multivariate cox regression models were used before and after adjusting for covariates including age, sex, previous stroke, diabetes mellitus, coronary artery disease, mean systolic blood pressure during the trial, congestive heart failure, alcohol use, carotid endarterectomy, smoking, body mass index, and stroke severity. Secondary analyses were performed with Cox regression models to assess whether there were any interactions between vitamin doses versus each of the other factors in predicting adverse vascular events among patients not using antplatelet medications.

Results
Among 3680 participants in the VISP trial, 1907 (52%) individuals were taking antplatelet medications. The group on antplatelet medications was equally matched with the group not on antplatelet medications with respect to stroke severity, demographic and vascular risk factors (Table 1). Subjects taking antplatelets, however, were less likely to smoke, more likely to take antlipid medications, and more likely to have a history of stroke before the index stroke.

For the group taking antplatelet medications, high-dose vitamin replacement therapy was associated with a higher risk of stroke when compared with low-dose vitamin therapy (hazard ratio [HR], 1.43; 95% confidence interval, 1.02–2.01; Table 2; Figure). On the contrary, among subjects not taking antplatelet medications, there was a trend toward lower risk of stroke among those who received high-when compared with those who received low-dose vitamins (HR, 0.86; 95% confidence interval, 0.62–1.19; Table 2; Figure). High-dose vitamin therapy did not affect the odds of the secondary outcome of stroke, MI, or vascular death regardless of antplatelet use.

The highest cumulative incidence of recurrent stroke occurred in subjects not taking antplatelet medications on low-dose vitamin therapy (Figure). Conversely, the lowest cumulative incidence of recurrent stroke occurred in subjects taking antplatelet medications and low-dose vitamin therapy. The risk of recurrent stroke was similar among (1) those taking antplatelet medications and high-dose vitamin therapy and (2) those not taking antplatelet medications but on high-dose vitamin therapy (Figure).

Discussion
In this retrospective analysis of the VISP trial, we found that high-dose B vitamin therapy was associated with a higher rate of recurrent stroke among individuals on antplatelet therapy. Individuals not on antplatelet therapy, however, tended to have a lower risk of recurrent stroke on high-dose B vitamin therapy.

The findings in this study corroborate the post hoc analysis of the VITATOPS trial. In VITATOPS, they found that

| Table 1. Descriptive Summary Statistics of Patients in VISP Trial (n=3680) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | No Antplatelet Use | Concurrent Antplatelet Use |
|                                 | Low-Dose Vitamin  | High-Dose Vitamin | Low-Dose Vitamin  | High-Dose Vitamin |
|                                 | n=892 | n=881 | n=961 | n=946 | P Value |
| Mean age, y                     | 65.7±0.4 | 66.1±0.4 | 66.7±0.3 | 66.6±0.3 | 0.068 |
| Sex, men, %                     | 61.7 | 59.8 | 63.8 | 64.6 | 0.0312 |
| Race, %                         |                     |                     |                     |                     |                   |
| White                           | 75.4 | 77.9 | 81.1 | 83.2 | … |
| Black                           | 17.3 | 16.6 | 13.7 | 11.9 | 0.0002 |
| Other                           | 7.3 | 5.6 | 5.2 | 4.9 | … |
| Hypertension, %                 | 72.9 | 73.7 | 73.9 | 74.9 | 0.4624 |
| Diabetes mellitus, %            | 28.6 | 26 | 32.9 | 28.7 | 0.0202 |
| Smoking, %                      | 18.3 | 19.1 | 12.9 | 17.5 | 0.005 |
| Antlipid use, %                 | 35.3 | 36 | 50.3 | 51.6 | <0.0001 |
| Previous stroke, %             | 17.9 | 15.9 | 27.9 | 30.4 | <0.0001 |
| NIHSS*                          | 0 | 31.7 | 33.1 | 35.4 | 34.1 | … |
| 1–4                             | 60.9 | 59.4 | 55.5 | 57.5 | 0.4438 |
| ≥5                              | 7.4 | 7.5 | 9.2 | 8.4 | … |
| Avg systolic BP, mmHg           | 140.7 | 142.5 | 140.5 | 139.8 | 0.0191 |
| Avg LDL†                       | 127.2 | 124.9 | 119.8 | 118.5 | 0.000 |
| Avg total cholesterol†          | 207.9 | 203.2 | 198.6 | 198.6 | 0.000 |

BP indicates blood pressure; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and VISP, Vitamin Intervention for Stroke Prevention.

*NIHSS as a marker for stroke severity.
†Cholesterol measured in mg/dL.

for participants taking antplatelets at baseline, B vitamins did not affect the primary outcome of stroke, MI, or death from vascular cause (HR, 0.94; 95% confidence interval, 0.83–1.07). However, for the participants not taking antplatelet drugs at baseline, B vitamins did have a significant effect on the primary outcome (HR, 0.76; 95% confidence interval, 0.60–0.96).

These findings have 2 potential ramifications. First, if patients with elevated homocysteine have a contraindication to antplatelet therapy, they may potentially benefit from taking high-dose B vitamin replacement therapy. Second, high-dose B vitamin therapy may need to be used with caution in those on antplatelet medications given the potentially deleterious effects.

The cause for the interaction between B vitamins and antplatelet medications remains unclear, but may be related to the roles of these compounds at the endothelium. At the endothelium, homocysteine inhibits nitric oxide, regulates prostanoioids, activates endothelin-1, activating angiotensin II receptors, and causing oxidative stress. By lowering homocysteine, B vitamins may reduce endothelial damage. Antplatelets inhibit platelet aggregation at the endothelium. Additional studies and scientific models are needed to elucidate the interaction between antplatelets and homocysteine.
This study has limitations. First, because this was a post hoc analysis of a clinical trial, it was not adequately powered for this subgroup analysis; therefore, any interactions seen could be because of chance. Second, the trial was performed in North America and Scotland during a time where folate fortification occurred. This lowered the baseline serum homocysteine and altered potential benefits of supplementing with B vitamins. A recent meta-analysis suggested that there is more likely to be risk reduction in trials lowering homocysteine when the baseline homocysteine is decreased by >20%. Third, because stroke subtypes were not predefined in this trial, we were not able to determine whether the group on antiplatelet medications was equally matched with the group not on antiplatelet medications with respect to stroke subtype. There remains a possibility that the interaction between vitamin replacement therapy and antiplatelet use occurred as a result of unbalanced stroke subtypes. Fourth, we were not able to differentiate between type and dose of antiplatelet used for all individuals during the trial. Fifth, as mentioned, the elevated stroke risk among individuals taking antiplatelets combined with high-dose B vitamins has not been noted previously and may be a spurious finding, given the wide confidence interval. Finally, the results of this study are not generalizable to all patients with stroke because the trial included individuals with only nondisabling, noncardioembolic stroke. Nevertheless, the strengths of the study include its rigorous trial design and detailed information on covariates.

Given the negative findings in 3 large RCTs, subgroup analyses have suggested that certain subgroups of individuals, such as younger individuals or those living in areas without folate fortification, may benefit from homocysteine lowering after stroke. The findings from this study, combined with the post hoc analysis from VITATOPS, suggest that individuals with contraindications to antiplatelet therapy may be another subgroup worthy of investigation in prospective RCTs of homocysteine lowering.

**Sources of Funding**

This study was supported by American Heart Association National Scientist Development Award.
Disclosures

None.

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*Stroke*. 2015;46:870-873; originally published online February 3, 2015;
doi: 10.1161/STROKEAHA.114.006927

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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