Effect of B Vitamins and Lowering Homocysteine on Cognitive Impairment in Patients With Previous Stroke or Transient Ischemic Attack

A Prespecified Secondary Analysis of a Randomized, Placebo-Controlled Trial and Meta-Analysis

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Background and Purpose—High plasma total homocysteine (tHcy) has been associated with cognitive impairment but lowering tHcy with B-vitamins has produced equivocal results. We aimed to determine whether B-vitamin supplementation would reduce tHcy and the incidence of new cognitive impairment among individuals with stroke or transient ischemic attack ≥6 months previously.

Methods—A total of 8164 patients with stroke or transient ischemic attack were randomly allocated to double-blind treatment with one tablet daily of B-vitamins (folic acid, 2 mg; vitamin B6, 25 mg; vitamin B12, 500 μg) or placebo and followed up for 3.4 years (median) in the VITAmins TO Prevent Stroke (VITATOPS) trial. For this prespecified secondary analysis of VITATOPS, the primary outcome was a new diagnosis of cognitive impairment, defined as a Mini-Mental State Examination (MMSE) score <24 on ≥2 follow-up visits. Secondary outcomes were cognitive decline, and the mean tHcy and MMSE at final follow-up.

Results—A total of 3089 participants (38%) voluntarily undertook the MMSE >6 months after the qualifying stroke; 2608 participants were cognitively unimpaired (MMSE ≥24), of whom 2214 participants (1110 B-vitamins versus 1104 placebo) had follow-up MMSEs during 2.8 years (median). At final follow-up, allocation to B-vitamins, compared with placebo, was associated with a reduction in mean tHcy (10.2 μmol/L versus 14.2 μmol/L; $P<0.001$) but no change from baseline in the mean MMSE score (−0.22 points versus −0.25 points; difference, 0.03; 95% confidence interval, −0.13 to 0.19; $P=0.726$) and no difference in the incidence of cognitive impairment (5.51% versus 5.47%; risk ratio, 1.01; 95% confidence interval, 0.69–1.48; $P=0.976$), cognitive decline (9.1% versus 10.3%; risk ratio, 0.89; 0.67–1.18; $P=0.414$), or cognitive impairment or decline (11.0% versus 11.3%; risk ratio, 0.98; 0.75–1.27; $P=0.855$).

Conclusions—Daily supplementation with folic acid, vitamin B6, and vitamin B12 to a self-selected clinical trial cohort of cognitively unimpaired patients with previous stroke or transient ischemic attack lowered mean tHcy but had no effect on the incidence of cognitive impairment or cognitive decline, as measured by the MMSE, during a median of 2.8 years.

Clinical Trial Registration—URL: http://www.controlled-trials.com. Unique identifier: ISRCTN74743444; URL: http://www.clinicaltrials.gov. Unique identifier: NCT00097669. **(*Stroke*. 2013;44:2232-2239.)**

Key Words: clinical trial ■ cognitive impairment ■ homocysteine ■ vitamin B complex

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Received April 21, 2013; accepted May 6, 2013.

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Ralph L. Sacco, MD, was guest editor for this article.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.001886/-/DC1.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.001886**

The world faces a looming epidemic of cognitive impairment and dementia.[1] Treatments that prevent, halt, or reverse cognitive impairment are needed. Several epidemiological studies report that high total plasma homocysteine (tHcy) concentration is an independent, significant risk factor for cognitive impairment and dementia,[2–7] but some do not.[8,9] A meta-analysis of 9 qualitatively good case–control studies found that the pooled mean tHcy was higher, by 1.04 μmol/L (95% confidence interval [CI], 0.44–1.63), among 631 patients with Alzheimer disease compared with 703 controls.[10] However, these studies are prone to confounding and reverse causality. Randomized trials of the effect of lowering tHcy with B-vitamins (folic acid, B12 and, to a lesser extent, B6) on cognitive decline minimize confounding and reverse causality but have produced conflicting or equivocal results.[11–28] The 2 trials that reported a benefit from lowering tHcy did so in subjects with elevated tHcy.[19,27]

In view of the uncertainty of the effect of lowering tHcy with B-vitamins on cognition, we aimed to assess, in a prespecified study, whether B-vitamin treatment would reduce the incidence of new cognitive impairment among cognitively unimpaired individuals with recent stroke or transient ischemic attack (TIA) of the brain enrolled in the VITAmins TO Prevent Stroke (VITATOPS) trial,[29,30] and whether the effect of B-vitamins on cognitive function may be augmented in, or limited to, participants with elevated tHcy. Secondary aims were to determine whether B-vitamin treatment would reduce the incidence of cognitive decline among cognitively impaired individuals with recent stroke or TIA in VITATOPS, and to add our results to a meta-analysis of all randomized controlled trials of B-vitamins on cognitive function.

Methods

The methods and primary results of the VITATOPS trial have been published.[29,30] The VITATOPS trial is registered with ClinicalTrials.gov, number NCT00097669, and Current Controlled Trials, number ISRCTN74743444.

Subjects and Design

Briefly, 8164 patients with recent stroke or TIA were randomly assigned to take B-vitamins (folic acid, 2 mg; vitamin B6, 25 mg; vitamin B12, 500 μg) or placebo for a median duration of 3·4 years (interquartile range, 2.0–5.5).[29,30] The primary outcome was the composite of stroke, myocardial infarction, or death from vascular causes.

This prespecified secondary study of VITATOPS, aimed at examining the effect of once daily B-vitamin treatments on the overall incidence of cognitive impairment and cognitive decline, was planned before the study began.[29] Hence, we collected cognitive outcomes throughout the study period.

Assessment of Cognitive Function

At randomization, and at follow-up 3 months and 6 months after randomization, and each 6 months thereafter, surviving participants were invited to undergo an optional Mini-Mental State Examination (MMSE). The MMSE is a brief test of 5 aspects of cognitive function (orientation, immediate and delayed recall, attention and concentration, language and visuospatial abilities) with ≈20% weight given to memory.[31]

Definitions of Cognitive Impairment and Decline

Cognitive impairment was defined as a new MMSE score <24, documented on ≥2 occasions after randomization and ≥6 months after the qualifying stroke.

Cognitive decline was defined as a decline of ≥3 points in the MMSE, compared with the baseline assessment at 6 months or more after the qualifying stroke, on ≥2 occasions during follow-up.

Assessment of tHcy

Investigators were encouraged, but not obligated, to take a fasting blood sample from consenting patients to measure blood concentrations of tHcy (fasting), red cell folate, vitamin B12, and creatinine at baseline, and at each follow-up visit.

Outcome Measures

The primary outcome for this prespecified secondary analysis was a new diagnosis of cognitive impairment (MMSE score <24 on ≥2 follow-up visits ≥6 months after the qualifying stroke).

Secondary outcomes were tHcy, the mean MMSE, a decline (from baseline, ≥6 months after stroke) of ≥3 points in the MMSE score on ≥2 follow-up visits (cognitive decline), and the composite of cognitive impairment and decline.

Statistical Methods

Baseline characteristics and laboratory data were tabulated according to subsequent MMSE testing or not, and assigned treatment groups, and expressed as proportions for categorical variables, and means (SD) for continuous variables with a normal distribution.

The primary analysis compared the incidence of new cognitive impairment between the placebo and B-vitamin groups during follow-up, by intention-to-treat. The event rates were calculated as the number of events that occurred during the follow-up period divided by the total number of patients randomized. The ratios of the event rates (risk ratio [RR]: treatment/placebo) and their 95% CIs were calculated to describe the treatment effect. A Cox proportional hazard model analysis was used to control for any potential imbalance in baseline characteristics and follow-up between the 2 groups.

Subgroup analyses compared the effect of B-vitamins with placebo on cognitive impairment and decline according to patient age at randomization, sex, ethnic group, clinical stroke syndrome, pathological and pathogenetic stroke subtype, folate fortification, diabetes mellitus, antiplatelet use, smoking, alcohol use, red cell folate concentrations, serum folate, tHcy concentrations, and years of follow-up.

Secondary analyses examined the association between baseline tHcy (where available) and subsequent cognitive impairment or decline, the change in the MMSE score between baseline and end of follow-up in each treatment group, and the incidence of cognitive decline in each treatment group among patients who were cognitively impaired at baseline. Two-sided significance tests were used throughout and a 2-sided P value <0.05 was considered significant.

Meta-analysis

We performed a systematic review of the PubMed, PsychINFO, Embase, and the Cochrane Collaboration database from inception to March 2013. We searched only published material, although study authors were contacted where clarification of published data was required for the purposes of the meta-analysis. Additional studies were sought from article reference lists, clinical trial registration websites, review articles, and conference abstracts.

The following search terms were used to source articles: homocysteine, homocystine, hyperhomocysteinemia, hyperhomocysteinaemia, B-vitamins, vitamin B12, vitamin B-12, cobalamin, cyanocobalamin, vitamin B6, vitamin B-6, pyridoxine, folate, folic acid, vitamin B9, vitamin B-9, memory, cognition, cognitive, Alzheimer, and dementia.

We performed a meta-analysis of 10 placebo-controlled, randomized trials of homocysteine-lowering B-vitamin supplementation of

individuals without and with cognitive impairment at the time of study entry, in which cognitive function was assessed by means of the MMSE.[31] For each study, the number of participants, mean change of MMSE score between baseline and study completion, and the SD of the change were recorded. Data were combined in a fixed-effects model and analyzed using RevMan release 5 (http://ims.cochrane.org/revman) to obtain a pooled summary estimate of effect across all trials.

Results

Cognitive Testing

Among the 8164 participants in VITATOPS, 3089 (38%) agreed to undertake the optional MMSE ≥6 months after the qualifying cerebrovascular event. Compared with those who did not have an MMSE, those who undertook the MMSE were older and more likely to be white, functionally independent, and have a TIA as the qualifying event (Table I in the online-only Data Supplement); there was no difference in the rate of recurrent stroke during follow-up.

Cognitively Unimpaired

Among the 3089 participants who undertook the MMSE ≥6 months after the qualifying cerebrovascular event, 481 participants (244 assigned B-vitamins versus 237 placebo) were cognitively impaired (MMSE <24), and 2608 participants were not cognitively impaired (MMSE ≥24). Of the 2608 participants who were not cognitively impaired, 2214 participants had ≥1 further MMSE measured during follow-up during a median of 2.8 years (interquartile range, 1.5–4.6; total range, 0–9 years).

The 2214 cognitively unimpaired participants who underwent subsequent cognitive testing were more likely to be white, have a qualifying TIA and lacunar syndrome at baseline (Table 1), and less likely to have experienced an early recurrent early stroke within 1 year of randomization (Table II in the online-only Data Supplement) compared with the 394 cognitively unimpaired participants who did not proceed to further cognitive testing. Table III in the online-only Data Supplement shows that there was no significant difference in the prevalence of baseline characteristics among the 2214 cognitively unimpaired participants allocated B-vitamins (n=1110) compared with placebo (1104), with the exception of atrial fibrillation (9.1% B-vitamins versus 6.5% placebo; P=0.022).

At final follow-up, allocation to B-vitamins, compared with placebo, was associated with a reduction in mean tHcy (10.2 [SD, 4.0] μmol/L B-vitamins, n=290 versus 14.2 [SD, 6.5] μmol/L placebo; n=289; P<0.0001) but no change in the mean MMSE score (27.73 [SD, 2.69] points B-vitamins versus 27.74 [SD, 2.77] points placebo; difference, 0.00; 95% CI, −0.23 to 0.22; P=0.97) and no change from baseline in the mean MMSE score (−0.22 points B-vitamins versus −0.25 points placebo; difference, 0.03; 95% CI, −0.13 to 0.19; P=0.726; Table IV in the online-only Data Supplement).

Table 2 shows that among the 2214 participants who were cognitively unimpaired at baseline and who subsequently undertook the MMSE (1110 B-vitamins, 1104 placebo), there was no significant difference in the incidence of cognitive impairment (5.51% B-vitamins versus 5.47% placebo; RR, 1.01; 95% CI, 0.69–1.48; P=0.976) among participants assigned B-vitamins compared with placebo. These results were consistent irrespective of the duration of follow-up, and if cognitive impairment was defined as MMSE <24 at the final follow-up visit. They were also consistent among participants with high tHcy (Figure V in the online-only Data Supplement), low red cell folate, cognitive impairment (MMSE <24) at baseline, and other clinical subgroups. However, if cognitive impairment was defined as an MMSE <24 at any time during final follow-up visit, there was a substantially greater number of cases of cognitive impairment (n=269 in both treatment groups versus 99 in both treatment groups if cognitive impairment was defined as MMSE <24 on 2 occasions) and a significant increase in cognitive impairment among participants assigned B-vitamins compared with placebo (RR, 1.29; 95% CI, 1.03–1.62).

Tables 3 and 4 show there was no significant difference in the incidence of cognitive decline (9.1% versus 10.3%; RR, 0.89; 95% CI, 0.67–1.18; P=0.414) or the composite of cognitive impairment and decline (11.0% versus 11.3%; RR, 0.98; 95% CI, 0.75–1.27; P=0.855) among participants assigned B-vitamins compared with placebo, respectively.

Cognitively Impaired

Table 5 shows the outcome of the 481 participants who were cognitively impaired (MMSE <24) at baseline, >6 months after the qualifying cerebrovascular event, according to treatment allocation. At final follow-up, allocation to B-vitamins, compared with placebo, was associated with a reduction in mean tHcy (9.6 [SD, 2.6] μmol/L B-vitamins, n=39 versus 16.9 [SD, 4.8] μmol/L placebo; n=37; P<0.0001) but no change from baseline in the mean MMSE score (0.72 [SD, 4.93] B-vitamins versus 1.12 [SD, 4.44] placebo; difference, 0.40; P=0.395) and no significant difference in the incidence of cognitive decline (9.0% versus 15.5%; P=0.095).

The Figure shows a meta-analysis of our VITATOPS study results together with the 10 randomized controlled trials of B-vitamins versus placebo in people without cognitive impairment (unimpaired) and with cognitive impairment (impaired) at baseline, which measured cognitive function as an outcome by means of the MMSE. Overall, B-vitamin supplementation did not improve cognitive function (standard mean difference=0.04; 95% CI, −0.09 to 0.17) compared with placebo.

Discussion

The principal finding of our study is that daily supplementation with folic acid, vitamin B6, and vitamin B12 in cognitively unimpaired patients with previous (>6 months) stroke or TIA significantly reduced mean tHcy but had no significant effect on the incidence of cognitive impairment or rate of cognitive decline during a median of 2.8 years. These results were consistent irrespective of tHcy at baseline.

The strengths of our study are that systematic bias in treatment allocation was minimized by randomization, and observer bias in the measurement of the MMSE was minimized by blinding of the participants and assessors to the treatment allocation.

Table 1. Baseline Characteristics in 2214 Cognitively Unimpaired Participants Who Voluntarily Undertook Subsequent Cognitive Function Testing by Means of the MMSE at >6 mo After the Qualifying Stroke vs the 394 Cognitively Unimpaired Participants Who Did Not Undergo Subsequent Cognitive Function Testing

Baseline Characteristics	With Subsequent MMSE (n=2214)	Without Subsequent MMSE (n=394)	*P* Value (χ^2)
Age, mean (SD)	63.6 (11.8)	62.8 (12.2)	0.2610
Sex, n (%)			
Males	1491 (67.3)	247 (62.7)	0.0710
Female	723 (32.7)	147 (37.3)	...
Ethnic group: n (%)			
White	1415 (64.8)	224 (58.3)	<0.0001
Asian	296 (13.6)	28 (7.3)	...
South Asian	253 (11.6)	109 (28.4)	...
Others	218 (10.0)	23 (6.0)	...
Oxfordshire classification, n (%)			
Total anterior circulation syndrome	20 (0.9)	11 (2.8)	0.0072
Partial anterior circulation syndrome	1201 (54.9)	220 (56.8)	...
Lacunar syndrome	793 (36.3)	124 (32.0)	...
Posterior circulation syndrome	173 (7.9)	32 (8.3)	...
Pathological subtype of stroke, n (%)			
Transient ischemic attack	604 (27.3)	76 (19.7)	0.0626
Ischemic stroke	1452 (65.7)	277 (71.8)	...
Intracerebral hemorrhage	93 (4.2)	20 (5.2)	...
Subarachnoid hemorrhage	22 (1.0)	4 (1.0)	...
Retinal infarction	10 (0.5)	2 (0.5)	...
Unknown/uncertain pathology	29 (1.3)	7 (1.8)	...
Pathogenetic subtype of stroke, n (%)			
Large artery disease	868 (39.7)	125 (32.5)	0.0004
Small artery disease	799 (36.5)	131 (34.0)	...
Embolism from the heart	96 (4.4)	19 (4.9)	...
Uncertain/unknown	299 (13.7)	84 (21.8)	...
Hemorrhagic event	127 (5.8)	26 (6.8)	...
Oxford Handicap Score			
Score ≤2, n (%)	1943 (89.6)	335 (87.0)	0.1348
Score ≥3, n (%)	226 (10.4)	50 (13.0)	...
Past history, n (%)			
Stroke	333 (15.1)	51 (13.2)	0.3291
Myocardial infarction	185 (8.4)	37 (9.6)	0.4541
Peripheral vascular disease	109 (4.9)	26 (6.8)	0.1354
Revascularization of brain, heart, or limbs	212 (9.6)	33 (8.4)	0.4520
Hypertension: ever	1522 (68.9)	267 (69.0)	0.9809
Hypertension: treated	1187 (54.0)	211 (54.7)	0.7966
Smoking: ever	1243 (56.3)	206 (53.4)	0.2811
Smoker: current	533 (24.2)	81 (20.9)	0.1638
Hypercholesterolemia: ever	913 (41.4)	130 (33.8)	0.0002
Hypercholesterolemia: treated	639 (29.1)	112 (29.2)	0.9867
Diabetes mellitus	423 (19.1)	92 (23.8)	0.0350
Atrial fibrillation	173 (7.8)	34 (8.8)	0.5058
Ischemic heart disease	401 (18.2)	62 (16.1)	0.3234
Past history of depression	189 (9.4)	41 (11.2)	0.2863
Alcohol: mean standard drinks per day (SD)	1.1 (3.0)	0.8 (1.6)	0.0175

MMSE indicates Mini-Mental State Examination.

Table 2. Incidence of New Cognitive Impairment (MMSE <24) >6 mo After the Qualifying Stroke According to Treatment Allocation

Mini-Mental State Examination (MMSE) Score	B-Vitamins		Placebo		RR (95% CI)	*P* Value (χ^2)
	n	%	n	%		
Baseline (>6 mo after qualifying stroke)						
≥24	1110		1104			
During follow-up on ≥2 occasions	908		895			
<24	50	5.51	49	5.47	1.01 (0.69–1.48)	0.9764
≥24	858	94.5	846	94.5		
During follow-up on any occasion	1110		1104			
<24	152	13.7	117	10.6	1.29 (1.03–1.62)	0.0258
≥24	958	86.3	987	89.4		
At the last follow-up	1110		1104			
<24	87	7.84	75	6.79	1.15 (0.86–1.55)	0.3455
≥24	1023		1029			

CI indicates confidence interval; and RR, risk ratio.

The limitations of our study include the use of the MMSE to define cognitive impairment and decline because the MMSE is susceptible to ceiling effects in high-functioning populations and has a low sensitivity for cognitive impairment.[32–34] However, it is likely to be a reasonably specific measure of cognitive impairment when applied as in our study (ie, a raw MMSE score ≤24 on ≥2 occasions is likely to indicate cognitive impairment in literate and educated patients).[33] Also, we did not record the educational status of the patients at the time of the MMSE, nor can we be sure that the patients did not have high-level language dysfunction or delirium at the time of the baseline and follow-up MMSE examinations. We endeavored to exclude patients whose cognitive function may have been compromised by the acute effects of the stroke by excluding MMSE examinations within 6 months of the qualifying stroke.

There are several other limitations that may have compromised the reliability and statistical power of our study to demonstrate a modest effect of B-vitamins, particularly among those with tHcy >11. First, the population of patients was a select group within a clinical trial cohort who had experienced a stroke ≥6 months previously and who were asked and volunteered to perform an MMSE examination. As expected, both baseline characteristics and subsequent stroke events influenced who volunteered for MMSE testing; participants who volunteered were less disabled (Tables I and II in the online-only Data Supplement). The presence of obvious cognitive impairment or poor educational status among a substantial proportion of enrolled stroke survivors may also have deterred investigators from testing the MMSE because the proportion of participants who did undergo MMSE and who scored <24 (18%; n=481) was lower than

Table 3. Incidence of Cognitive Decline (MMSE ≥3) >6 mo After the Qualifying Stroke According to Treatment Allocation

Mini-Mental State Examination (MMSE) Score	B-Vitamins		Placebo		RR (95% CI)	*P* Value (χ^2)
	n	%	n	%		
Baseline (>6 mo after qualifying stroke)						
≥24	1110		1104			
During follow-up on ≥2 occasions	908		895			
≥3	83	9.1	92	10.3	0.89 (0.67–1.18)	0.4143
<3	825	90.9	803	89.7		
During follow-up on any occasion	1110		1104			
≥3	252	22.7	228	20.7	1.10 (0.94–1.29)	0.2417
<3	858	77.3	876	79.4		
At the last follow-up	1110		1104			
≥3	135	12.2	127	11.5	1.06 (0.84–1.33)	0.6315
<3	975	87.8	977	88.5		

CI indicates confidence interval; and RR, risk ratio.

Table 4. Incidence of the Composite of New Cognitive Impairment (MMSE <24) or Decline (MMSE ≥3) >6 mo After the Qualifying Stroke According to Treatment Allocation

Mini-Mental State Examination (MMSE) Score	B-Vitamins		Placebo		RR (95% CI)	*P* Value (χ^2)
	n	%	n	%		
Baseline (>6 mo after qualifying stroke)						
≥24	1110		1104			
During follow-up on ≥2 occasions	908		895			
<24 and decline ≥3	100	11.0	101	11.3	0.98 (0.75–1.27)	0.8546
≥24 or decline <3	808	89.0	794	88.7		
During follow-up on any occasion	1110		1104			
<24 and decline ≥3	273	24.6	240	21.7	1.13 (0.97–1.32)	0.1113
≥24 or decline <3	837	75.4	864	78.3		
At the last follow-up	1110		1104			
<24 and decline ≥3	152	13.7	140	12.7	1.08 (0.87–1.34)	0.4814
≥24 or decline <3	958	86.3	964	87.3		

CI indicates confidence interval; and RR, risk ratio.

the expected prevalence of 30% for a general population of stroke survivors.[35] Consequently, we cannot confidently generalize our results of a lack of effect of B-vitamin treatment on cognitive function in 481 participants to all people with established cognitive impairment. The low proportion of participants volunteering for MMSE (38%) may also reflect the reality that patients were assessed at follow-up by busy clinicians who volunteered their time to this study, and whose main priority was to establish safety of the trial medication and survival free of the primary outcome (stroke, myocardial infarction, or vascular death), rather than optional secondary outcomes such as cognitive function. Second, the primary outcome required a new MMSE reading <24 on ≥2 occasions during follow-up. We chose not to rely on a single MMSE reading <24 because this could have reflected a solitary poorer performance attributable to random error (chance) or intercurrent illness (delirium). However, by adopting this stricter definition of cognitive impairment, we probably failed to include some cases of true cognitive impairment who were not followed up for long enough to record a second MMSE <24. Nevertheless, among all of our definitions of cognitive impairment, there was no benefit of vitamins, and there was only one outcome in which B-vitamins were associated with a significant increase in cognitive impairment (MMSE <24 on any occasion during follow-up); we suspect this result reflects random error (chance) because it is a solitary measure that is inconsistent with all the other results. Third, follow-up MMSEs are likely to have been performed by the more healthy survivors among the cohort and, hence, are prone to a healthy survivor bias; those with cognitive decline and impairment may have been more likely to not attend for follow-up or to persevere with a voluntary MMSE at follow-up. The results were not changed, however, if we redefined cognitive impairment as an MMSE <24

Table 5. Outcome of the 481 Participants Who Were Cognitively Impaired (MMSE <24) at Baseline (>6 mo After the Qualifying Cerebrovascular Event) According to Treatment Allocation

Outcome	B-Vitamins n=244	Placebo n=237	*P* Value (χ^2)
Last follow-up tHcy, mean (SD)	9.6 (2.6) (n=39)	16.9 (4.8) (n=37)	<0.0001
Mean MMSE during follow-up, mean (SD)	20.5 (5.1)	21 (4.7)	0.3263
Mean difference in MMSE between baseline and final follow-up (final, baseline)	0.72 (4.93)	1.12 (4.44)	0.3948
During follow-up on ≥2 occasions			
≥3 (MMSE decline by ≥3)	13 (9.0)	22 (15.5)	0.0953
<3	131	120	
During follow-up on any occasion, n (%)			
≥3 (MMSE decline by ≥3)	50 (25.6)	56 (28.9)	0.4751
<3	145	138	
At the last follow-up, n (%)			
≥3 (MMSE decline by ≥3)	41 (21.0)	40 (20.6)	0.9212
<3	154	154	

MMSE indicates Mini-Mental State Examination; and tHcy, total homocysteine.

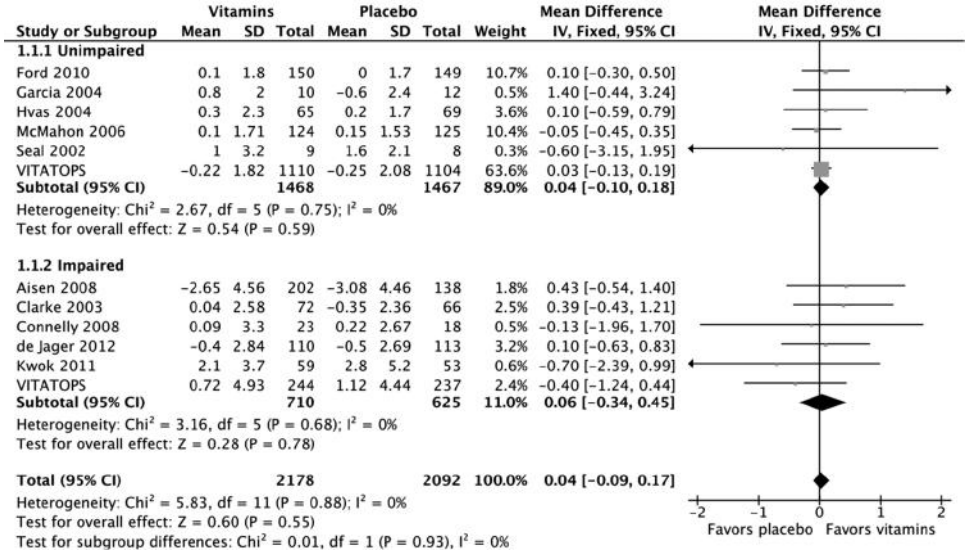

Figure. Forest plot of randomized controlled trials of B-vitamins vs placebo in cognitively unimpaired and impaired people, which measured cognitive function as an outcome by means of the Mini-Mental State Examination (MMSE). The left of the plot shows the mean differences in MMSE score between baseline and the end of follow-up for each treatment group within each study, and the right of the plot shows an estimate of mean difference and its 95% confidence interval (CI) among participants allocated B-vitamins vs placebo for each study. The bottom of the plot shows a total result for all trials pooled.

on one occasion followed by death or recurrent stroke, or cognitive decline as a reduction in the MMSE by ≥3 points from baseline on one occasion followed by death or recurrent stroke.

Despite the above limitations, our results in patients with previous stroke are consistent with other randomized trials of homocysteine-lowering treatment for cognitive decline among cognitively unimpaired and impaired older people without stroke (Figure).[10–27] Furthermore, our results more than double the current database, adding data from 2214 patients to a previous pool of 721 cognitively unimpaired patients and 481 patients to a previous pool of 854 cognitively impaired patients, and thereby substantially increase the precision of the estimate of the effect of B-vitamins on cognitive function as measured by the MMSE.

The implications of the results of our trial and other trials in the meta-analysis for clinicians are that daily supplementation with folic acid, vitamin B6, and vitamin B12 to a self-selected clinical trial cohort of cognitively unimpaired patients with previous (>6 months) stroke or TIA does not have a demonstrably clinically useful effect on the incidence of cognitive impairment or rate of cognitive decline, as measured by the MMSE, during the next few years.

Acknowledgments

Dr Hankey initiated the analysis for this substudy and wrote the first and final drafts of the report. Dr Ford performed the meta-analysis. Dr Yi did all other analyses. Drs Eikelboom, Lees, Chen, Xavier, Navarro, Ranawaka, Uddin, Ricci, Gommans, Schmidt, Almeida, and van Bockxmeer contributed to each draft of the report. All authors with the exception of Drs Ford and Almeida were members of the International Steering Committee of the VITAmins TO Prevent Stroke (VITATOPS) trial.

Sources of Funding

The VITAmins TO Prevent Stroke (VITATOPS) trial was funded by the National Health and Medical Research Council of Australia, the UK Medical Research Council, the Biomedical Research Council of Singapore, the National Medical Research Council of Singapore, the National Heart Foundation of Australia, the Royal Perth Hospital Medical Research Foundation, and the Health Department of Western Australia. Blackmores, Australia, supplied the B vitamin and matching placebo tablets.

Disclosures

None.

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