B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial

*The VITATOPS Trial Study Group**

Summary

Background Epidemiological studies suggest that raised plasma concentrations of total homocysteine might be a risk factor for major vascular events. Whether lowering total homocysteine with B vitamins prevents major vascular events in patients with previous stroke or transient ischaemic attack is unknown. We aimed to assess whether the addition of once-daily supplements of B vitamins to usual medical care would lower total homocysteine and reduce the combined incidence of non-fatal stroke, non-fatal myocardial infarction, and death attributable to vascular causes in patients with recent stroke or transient ischaemic attack of the brain or eye.

Methods In this randomised, double-blind, parallel, placebo-controlled trial, we assigned patients with recent stroke or transient ischaemic attack (within the past 7 months) from 123 medical centres in 20 countries to receive one tablet daily of placebo or B vitamins (2 mg folic acid, 25 mg vitamin B6, and 0·5 mg vitamin B12). Patients were randomly allocated by means of a central 24-h telephone service or an interactive website, and allocation was by use of random permuted blocks stratified by hospital. Participants, clinicians, carers, and investigators who assessed outcomes were masked to the assigned intervention. The primary endpoint was the composite of stroke, myocardial infarction, or vascular death. All patients randomly allocated to a group were included in the analysis of the primary endpoint. This trial is registered with ClinicalTrials.gov, NCT00097669, and Current Controlled Trials, ISRCTN74743444.

Findings Between Nov 19, 1998, and Dec 31, 2008, 8164 patients were randomly assigned to receive B vitamins (n=4089) or placebo (n=4075). Patients were followed up for a median duration of 3·4 years (IQR 2·0–5·5). 616 (15%) patients assigned to B vitamins and 678 (17%) assigned to placebo reached the primary endpoint (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). There were no unexpected serious adverse reactions and no significant differences in common adverse effects between the treatment groups.

Interpretation Daily administration of folic acid, vitamin B6, and vitamin B12 to patients with recent stroke or transient ischaemic attack was safe but did not seem to be more effective than placebo in reducing the incidence of major vascular events. These results do not support the use of B vitamins to prevent recurrent stroke. The results of ongoing trials and an individual patient data meta-analysis will add statistical power and precision to present estimates of the effect of B vitamins.

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Introduction

After an ischaemic stroke or transient ischaemic attack of the brain or eye, patients remain at increased risk of future stroke, myocardial infarction, or vascular death (major vascular events) despite use of medical and surgical therapies.[1] Cross-sectional and observational epidemiological studies suggest that raised plasma concentrations of total homocysteine are a common causal risk factor for major vascular events.[2–4] Furthermore, randomised trials show that total homocysteine can be lowered by supplementary treatment with B vitamins: 0·5–5·0 mg folic acid daily lowers total homocysteine by 25% (95% CI 23–28%) and 0·02–1·00 mg vitamin B12 (mean 0·50 mg) daily lowers total homocysteine by 7% (3–10%).[5] However, whether lowering total homocysteine prevents major vascular events in patients with stroke and transient ischaemic attack is unknown. There have been no placebo-controlled trials of B vitamins in patients with stroke or transient ischaemic attack. The only previous randomised trial of treatment with B vitamins in patients with a history of stroke—the Vitamins Intervention for Stroke Prevention (VISP) trial[6]—compared high-dose B vitamins (25 mg pyridoxine, 0·4 mg cobalamin, and 2·5 mg folic acid) with low-dose B vitamins (200 µg pyridoxine, 6 µg cobalamin, and 20 µg folic acid) and was stopped because of futility after 3680 patients had been followed up for a mean of 20 months. There was no difference in the primary outcome of cerebral infarction between the groups (risk ratio [RR] 1·0, 95% CI 0·8–1·3), despite a mean reduction of total homocysteine of 2 µmol/L among patients assigned to high-dose B vitamins compared with

those assigned to low-dose B vitamins.[6] However, in an efficacy analysis of 2155 patients who were deemed most likely to benefit from treatment with B vitamins (ie, excluding patients with low vitamin B12 concentrations who were unable to absorb oral vitamin B12 and patients with high vitamin B12 concentrations who were already taking a vitamin B12 supplement), there was a 21% (95% CI 0–37%) reduction in the combined outcome of ischaemic stroke, coronary disease, or death in patients assigned to high-dose B vitamins compared with those assigned to low-dose B vitamins.[7]

Trials in other populations of patients have not shown a significant benefit of B vitamins compared with placebo in reducing major vascular events.[8–22] This absence of detectable benefit has several possible explanations: there might have been too few outcome events to provide sufficient statistical power for a modest but clinically important effect to be reliably identified or excluded; the doses of B vitamins might have been too low; the duration of treatment with B vitamins might have been too short; results might have been affected by food concurrently being fortified with folic acid; and, if total homocysteine is a marker and not a cause of vascular risk, lowering total homocysteine might have no effect on vascular risk.

The VITAmins TO Prevent Stroke (VITATOPS) trial aimed to test the hypothesis that the addition of once-daily supplements of B vitamins to usual medical care would reduce the combined incidence of non-fatal stroke, non-fatal myocardial infarction, and death attributable to vascular causes among patients with recent stroke or transient ischaemic attack of the brain or eye.[23,24]

For the **interactive website** see http://vitatops.highway1.com.au

Methods

Patients

For the **trial protocol** see http://vitatops.highway1.com.au/html/index.asp?section=pro

The rationale and design of the VITATOPS trial have been published previously.[23,24] Briefly, VITATOPS was a prospective, randomised, double-blind, placebo-controlled clinical trial involving 123 medical centres in 20 countries from four continents. VITATOPS was undertaken in accordance with the Declaration of Helsinki and the CONSORT guidelines.[25,26]

Patients were eligible for inclusion if they had had a stroke (ischaemic or haemorrhagic) or transient ischaemic attack (eye or brain), as defined by standard criteria,[27] within the past 7 months. Patients with haemorrhagic stroke were included because the underlying cause is frequently intracranial small vessel disease[27] and the prognosis can include ischaemic strokes and coronary events that might respond to B-vitamin therapy.[28,29] We chose the cutoff of 7 months to allow for the inclusion of patients who had already been enrolled in an acute stroke treatment trial and who needed to complete the final 6-month follow-up for that trial before they could be eligible to enrol in other trials, such as VITATOPS. Patients were excluded if they were taking folic acid, vitamin B6, vitamin B12, or a folate antagonist (eg, methotrexate); if they were pregnant or were women of childbearing potential; or if they had a limited life expectancy (eg, because of ill health).

The trial received ethics approval from national (India, New Zealand, and the UK) and local research ethics committees and all patients provided written informed consent before enrolment.[24]

Randomisation and masking

Patients were randomly assigned to receive either B vitamins (2 mg folic acid, 25 mg vitamin B6, and 0·5 mg vitamin B12) or matching placebo that had the same colour and coating. Random allocation was done by use of a central 24 h telephone service or an interactive website by use of random permuted blocks stratified by hospital. Patients, clinicians, trial coordinators, and outcome investigators were masked to treatment allocation. The data monitoring and safety committee, who were unmasked to treatment allocation, reviewed the safety data every 6 months and reported to the steering committee.

Procedures

Demographic and clinical characteristics of the participants were recorded at baseline. Investigators were encouraged, but not obligated, to take a fasting blood sample from

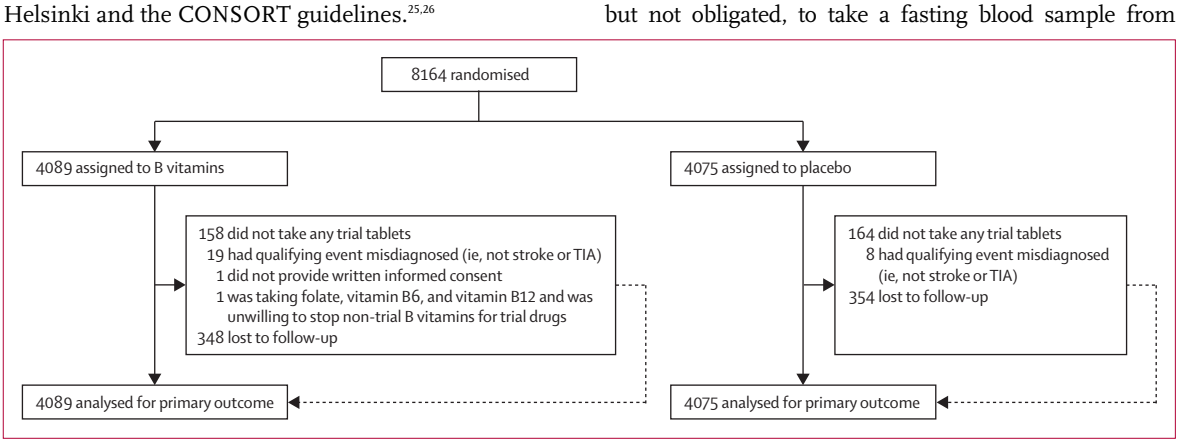

Figure 1: **Trial profile**
TIA=transient ischaemic attack.

consenting patients to measure blood concentrations of total homocysteine (fasting), red cell folate, vitamin B12, and creatinine. Patients were followed up every 6 months after random allocation until completion of the trial.

The primary outcome was the composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular causes, whichever occurred first. Secondary outcomes were stroke (non-fatal or fatal); myocardial infarction (non-fatal or fatal); death from any vascular cause; death from any cause; revascularisation procedures; the composite of non-fatal stroke, non-fatal myocardial infarction, and death from any vascular cause; and revascularisation procedures of the coronary, cerebral, or peripheral circulation. All investigator-reported outcomes and adverse events were audited by a masked adjudication committee.

Statistical analysis

Our sample size calculations were based on equally sized intervention and placebo groups, a minimum follow-up of 6 months for the last patient to be randomly allocated, an annual primary outcome event rate of 8% in the placebo group,[30] and a 15% decrease in the relative risk of the primary outcome among patients assigned to B vitamins (ie, 6·8% per year) compared with placebo. For a type 1 error of 5% and type 2 error of 20%, and assuming a mean follow-up of 2 years, a sample size of 3982 patients was required in each treatment group.

When recruitment began in November, 1998, we planned to complete the trial by the end of 2004.[23] Patients were therefore asked to consent to 5 years of follow-up. In 2004, when the initial patients had completed 5 years of follow-up, 4000 of the target of 7964 patients had been enrolled, and the primary outcome event rate in the trial population was 5·1% rather than 6·8–8%. While still masked to the event rates in each treatment group, the steering committee decided to increase the sample size and extend the duration of follow-up until at least 26 000 patient-years of follow-up had been achieved in the whole trial population. Patients were therefore asked to consent to ongoing follow-up beyond 5 years until the trial ended.

All data analyses were done according to a pre-established analysis plan.[23,24] Baseline characteristics and laboratory data were tabulated according to the assigned treatment groups, and were expressed as proportions for categorical variables and as means (SD) for continuous variables with a normal distribution.

All patients randomly allocated to a group were included in the primary analysis.[31] We used Kaplan-Meier methods to construct cumulative time-to-event curves for the two groups, with a comparison by use of the log-rank test.[32] We used a Cox proportional hazard model analysis to control for any potential imbalance in baseline characteristics and follow-up between the two groups.[33] We also used a random effects model (frailty model) to investigate the possible influence of any variation in treatment effect among the various centres.[33]

	B vitamins (n=4089)		Placebo (n=4075)		Total (n=8164)	
	Total	Value	Total	Value	Total	Value
Age	4089	62·5 (12·6)	4075	62·6 (12·4)	8164	62·6 (12·5)
Men	4089	2614 (64%)	4075	2604 (64%)	8164	5218 (64%)
Ethnic group						
White	3916	1638 (42%)	3898	1638 (42%)	7814	3276 (42%)
East and southeast Asian	3916	956 (24%)	3898	957 (25%)	7814	1913 (24%)
South Asian	3916	1037 (26%)	3898	1016 (26%)	7814	2053 (26%)
Other	3916	285 (7%)	3898	287 (7%)	7814	572 (7%)
Oxfordshire classification of stroke subtype						
Total anterior circulation syndrome	4011	90 (2%)	4000	103 (3%)	8011	193 (2%)
Partial anterior circulation syndrome	4011	2153 (54%)	4000	2153 (54%)	8011	4306 (54%)
Lacunar syndrome	4011	1522 (38%)	4000	1513 (38%)	8011	3035 (38%)
Posterior circulation syndrome	4011	246 (6%)	4000	231 (6%)	8011	477 (6%)
Pathological subtype of stroke						
Ischaemic stroke						
Transient ischaemic attack of brain or eye	4049	687 (17%)	4037	715 (18%)	8086	1402 (17%)
Ischaemic stroke	4049	2860 (71%)	4037	2843 (70%)	8086	5703 (71%)
Retinal infarction	4049	7 (0%)	4037	11 (0%)	8086	18 (0%)
Haemorrhagic stroke						
Primary intracerebral haemorrhage	4049	384 (9%)	4037	358 (9%)	8086	742 (9%)
Subarachnoid haemorrhage	4049	32 (1%)	4037	34 (1%)	8086	66 (1%)
Uncertain or unknown pathological type	4049	79 (2%)	4037	76 (2%)	8086	155 (2%)
Cause of ischaemic stroke						
Large artery disease	3590	1499 (42%)	3606	1525 (42%)	7196	3024 (42%)
Small artery disease	3590	1374 (38%)	3606	1388 (38%)	7196	2762 (38%)
Embolism from the heart	3590	216 (6%)	3606	186 (5%)	7196	402 (6%)
Uncertain or unknown cause	3590	501 (14%)	3606	507 (14%)	7196	1008 (14%)
Severity of qualifying stroke						
Independent (Oxford handicap score <3)	3986	3035 (76%)	3967	3024 (76%)	7953	6059 (76%)
Dependent (Oxford handicap score ≥3)	3986	951 (24%)	3967	943 (24%)	7953	1894 (24%)
Past history						
Stroke	4035	624 (15%)	4028	658 (16%)	8063	1282 (16%)
Myocardial infarction	4027	298 (7%)	4018	300 (7%)	8045	598 (7%)
Peripheral artery disease	4034	179 (4%)	4023	188 (5%)	8057	367 (5%)
Revascularisation procedure of brain, heart, or limbs	4089	275 (7%)	4075	292 (7%)	8164	567 (7%)
History of hypertension	4035	2863 (71%)	4027	2874 (71%)	8062	5737 (71%)
Ever smoked	4032	2011 (50%)	4026	2008 (50%)	8058	4019 (50%)
Hypercholesterolaemia	4026	1333 (33%)	4021	1321 (33%)	8047	2654 (33%)
Diabetes	4039	954 (24%)	4028	945 (23%)	8067	1899 (24%)
Atrial fibrillation	4036	330 (8%)	4027	318 (8%)	8063	648 (8%)
Ischaemic heart disease	3917	658 (17%)	3905	671 (17%)	7822	1329 (17%)
History of depression	3642	273 (8%)	3635	271 (7%)	7278	544 (7%)
Alcohol intake (standard drinks [10 g alcohol] per day)	4088	0·8 (2·3)	4074	0·8 (2·6)	8162	0·8 (2·5)

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	B vitamins (n=4089)		Placebo (n=4075)		Total (n=8164)	
	Total	Value	Total	Value	Total	Value
(Continued from previous page)						
Laboratory results						
Creatinine (μmol/L)	2214	92·4 (40·3)	2180	91·4 (34·6)	4394	91·9 (37·6)
Vitamin B12 (pmol/L)	243	320 (166)	251	325 (197)	494	322 (182)
Vitamin B6 (nmol/L)	208	40·5 (21·2)	204	38·7 (19·0)	412	39·6 (20·1)
Red cell folate (nmol/L)	209	962 (495)	202	881 (453)	411	922 (476)
Fasting homocysteine (μmol/L)	604	14·4 (9·2)	601	14·2 (7·7)	1205	14·3 (8·5)
Creatinine >120 μmol/L*	2214	253 (11%)	2180	240 (11%)	4394	493 (11%)
Median vitamin B12 ≤287 pmol/L†	243	126 (52%)	251	122 (49%)	494	248 (50%)

Data are mean (SD) or number (%). *Cutoff value chosen because 120 μmol/L is the upper limit of normal in many laboratories. †Cutoff value chosen because 287 pmol/L was the median value.

Table 1: **Demographics and baseline characteristics**

	B vitamins (n=4089)	Placebo (n=4075)	Risk ratio (95% CI)	p value*
Primary				
Stroke, myocardial infarction, or vascular death	616 (15%)	678 (17%)	0·91 (0·82–1·00)	0·05
Secondary				
Stroke	360 (9%)	388 (10%)	0·92 (0·81–1·06)	0·25
Myocardial infarction	118 (3%)	114 (3%)	1·03 (0·80–1·33)	0·86
Vascular death	328 (8%)	380 (9%)	0·86 (0·75–0·99)	0·04
Non-vascular death	267 (7%)	231 (6%)	1·15 (0·97–1·37)	0·14
Death from any cause	614 (15%)	633 (16%)	0·97 (0·87–1·07)	0·49
Stroke, myocardial infarction, or any death	851 (21%)	887 (22%)	0·96 (0·88–1·04)	0·26
Revascularisation procedure	122 (3%)	113 (3%)	1·08 (0·84–1·38)	0·57
Stroke, myocardial infarction, vascular death, or revascularisation	684 (17%)	740 (18%)	0·92 (0·84–1·01)	0·09

Data are number (%). Only the first event was used for each type of event. One patient could have multiple different types of event, so the sum of myocardial infarction, stroke, and death could be more than the total of the primary outcome. *Log-rank test.

Table 2: **Efficacy outcomes**

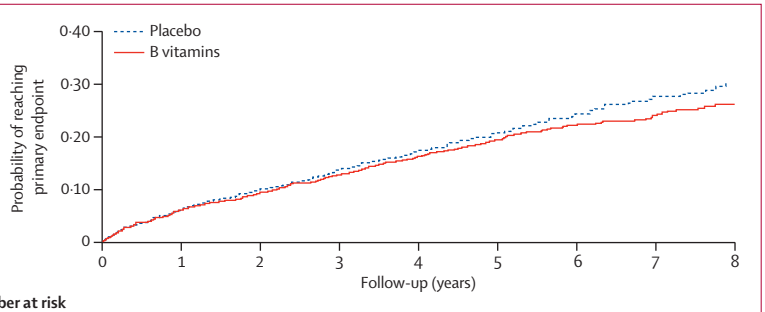

Figure 2: **Kaplan-Meier estimates of the composite primary outcome**
Risk ratio 0·91 (95% CI 0·82–1·00).

See Online for webappendix

In prespecified subgroup analyses we compared the primary outcome between the placebo group and the B vitamins group according to age, sex, ethnic group, clinical stroke syndrome, stroke pathology, stroke cause, stroke severity, baseline blood creatinine, total homocysteine, and vitamin B12 status.[24] We also did a prespecified secondary on-treatment analysis that excluded any patients who did not take any of the trial drugs or who did not comply with the protocol. We used two-sided significance tests throughout and p 0·05 was deemed significant.

This trial is registered with ClinicalTrials.gov, NCT00097669, and Current Controlled Trials, ISRCTN74743444.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 19, 1998, and Dec 31, 2008, 8164 patients were randomly assigned to receive B vitamins (n=4089) or placebo (n=4075; figure 1). Demographics and baseline characteristics were similar between groups (table 1). 42% of patients were white, 24% east or southeast Asian, and 26% south Asian. The qualifying diagnosis was ischaemic stroke in 71% of patients, transient ischaemic attack in 17%, and intracerebral haemorrhage in 9%. 76% of patients were functionally independent (Oxford handicap score ≤2) at the time of random allocation.[34]

Patients were followed up until June 30, 2009, with 14 182 person-years of follow-up in the B vitamins group and 13 997 person-years of follow-up in the placebo group. The median duration of follow-up was 3·4 years (IQR 2·0–5·5). 7462 (91%) of 8164 patients were followed up until the trial ended; 702 patients (9%) were lost to follow-up, primarily at three sites (n=392; 56%). The rate of loss to final follow-up was 8·7% in the placebo group and 8·5% in the B vitamins group (webappendix p 1). 1543 (38%) of 4079 patients who were randomly assigned before June 30, 2004, who had consented to 5 years of follow-up, and who were invited to continue follow-up beyond 5 years chose to stop the study drug and withdrew consent for further follow-up.

The rate of discontinuation of trial drugs increased with time, and at the same rate in each treatment group (p=0·51). In the first year, 414 (10%) of 4075 patients assigned placebo and 436 (11%) of 4089 assigned B vitamins had discontinued, and at the end of the trial 1115 (27%) of 4075 patients in the placebo group and 1148 (28%) of 4089 in the B vitamins group had discontinued (webappendix p 1).

The composite primary endpoint of non-fatal stroke, non-fatal myocardial infarction, or vascular death occurred in 616 (15%) of 4089 patients in the B vitamins group (4·3% per year) and in 678 (17%) of 4075 patients

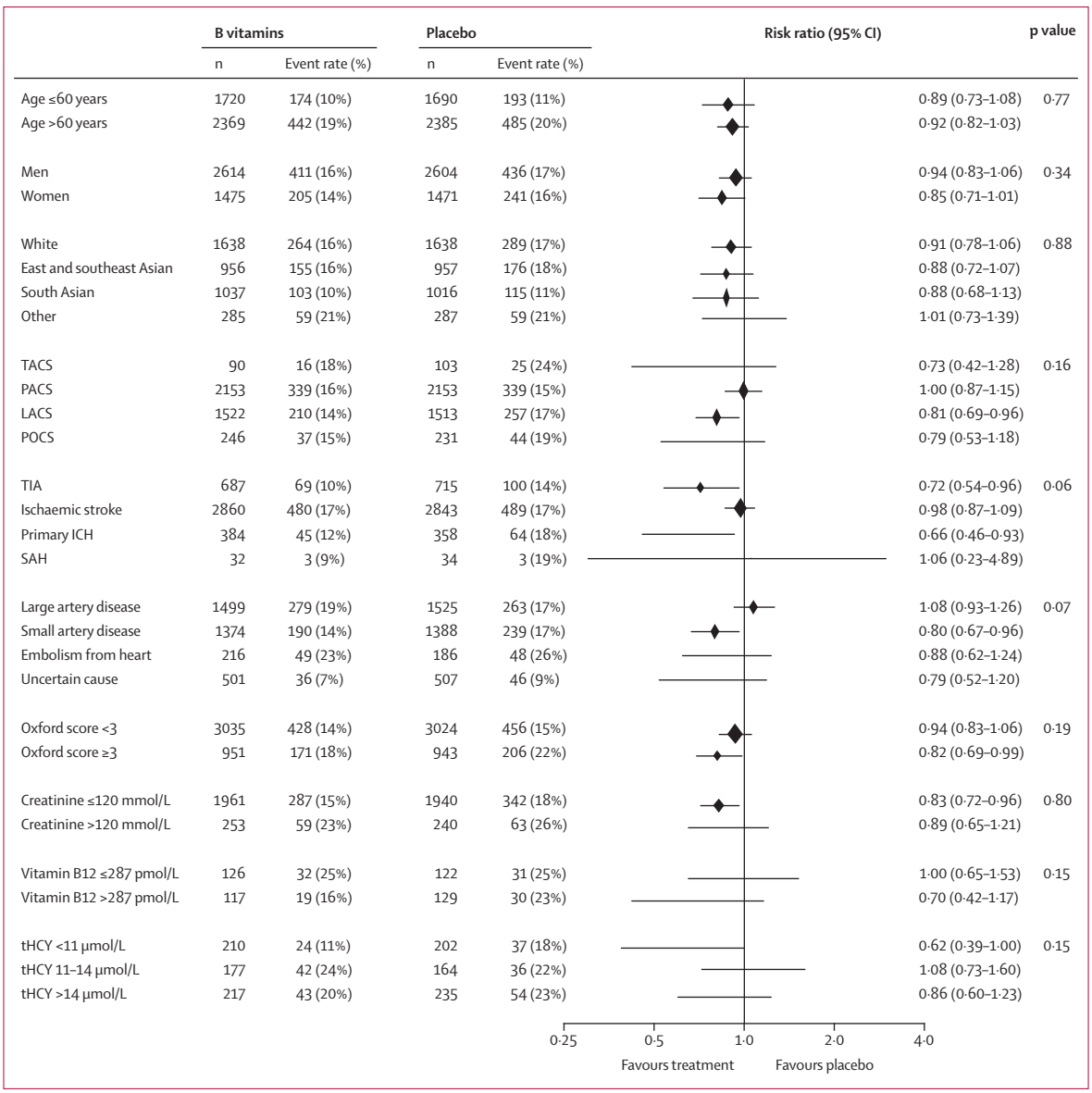

Figure 3: **Effects of B vitamins on the primary outcome in prespecified subgroups**
TACS=total anterior circulation syndrome. PACS=partial anterior circulation syndrome. LACS=lacunar syndrome. POCS=posterior circulation syndrome. TIA=transient ischaemic attack. ICH=intracerebral haemorrhage. SAH=subarachnoid haemorrhage. Oxford score=Oxford handicap score.[34] tHCY=total homocysteine. To convert values for creatinine from mmol/L to mg/L, divide by 88·4. To convert values for vitamin B12 from pmol/L to pg/mL, divide by 0·7378. To convert values for homocysteine from µmol/L to mg/L, divide by 7·396.

in the placebo group (4·8% per year; RR 0·91, 95% CI 0·82 to 1·00; p=0·05; absolute risk reduction 1·56%, 95% CI –0·01 to 3·16; table 2; figure 2). A Cox proportional hazard model analysis revealed similar hazard ratios to the RR, both before (0·90, 95% CI 0·81 to 1·00) and after (0·91, 0·81 to 1·03) adjusting for any potential imbalance in the baseline characteristics and follow-up duration between the two groups. In a random effects (frailty) model that was fitted to take into account any variation in treatment effect between centres, the fixed treatment effect (hazard ratio 0·90, 95% CI 0·81 to 1·00) was consistent with that derived from the Cox model.

Compared with placebo, treatment with B vitamins was not associated with a significant reduction in the RR for non-fatal or fatal stroke (p=0·25), non-fatal or fatal myocardial infarction (p=0·86), or death from any cause (p=0·49) but was associated with a significant reduction in death from vascular causes (p=0·04; table 2). For the prespecified subgroups, there was no inconsistency or significant interaction with the overall treatment effect of B vitamins (figure 3).

Among 1164 patients who had a fasting blood test at the end of follow-up, the mean total homocysteine concentration was 10·5 µmol/L (SD 4·9) in the

B vitamins group and 14·3 µmol/L (6·1) in the placebo group (difference 3·8 µmol/L, 95% CI 3·1–4·4; p<0·0001). The blood samples were taken mainly in Australia (438 patients; 38%), Singapore (344; 30%), and Austria (157; 13%). The effect of B vitamins on total homocysteine was similar in patients from these countries and those from other countries (data not shown).

925 patients had a fasting blood test for total homocysteine at both baseline and follow-up. Total homocysteine decreased by a mean of 1·09 (SD 5·5) µmol/L between baseline and follow-up, and 198 patients reached the primary endpoint. Cox regression analysis revealed that for every 1·0 µmol/L decrease in total homocysteine, the risk of the primary outcome decreased by 2·0% (95% CI –0·5 to 4·3; hazard ratio 0·98, 95% CI 0·96 to 1·01; p=0·11).

In a post-hoc secondary exploratory analysis that excluded the three sites from which 56% of the patients were lost to follow-up, the unadjusted relative risk of the primary outcome for the remaining 6789 patients was 0·91 (95% CI 0·81–1·01; p=0·073) and the adjusted RR was 0·91 (95% CI 0·80–1·03; p=0·14), which was consistent with that for the whole trial population. The results of the on-treatment analysis—which excluded 351 patients because of a protocol violation or because the patient did not take any of the trial drugs—were also consistent with the results from the whole trial population (webappendix p 2).

Vitamin B12 deficiency was diagnosed during follow-up in none of the 4089 patients in the B vitamins group compared with six (0·1%) of 4075 patients in the placebo group (p=0·02). Peripheral neuropathy suspected to be caused by vitamin B6 toxicity was diagnosed in five patients assigned to B vitamins (0·1%) compared with nine patients assigned to placebo (0·2%; p=0·30). There were no unexpected serious and non-serious adverse events and there were no significant differences in common adverse effects between the treatment groups (data not shown).

Discussion

In the VITATOPS trial, daily treatment with the combination of folic acid, vitamin B6, and vitamin B12 after a recent stroke or transient ischaemic attack was safe but was not significantly more effective than placebo in reducing the incidence of major vascular events. Our results are generalisable because we included a large number of patients from various ethnic groups from around the world who were not exposed to mandatory background fortification of food with folic acid.

On the basis of an interpretation of the epidemiological evidence available when we designed the study,[2,5,23,24] we hypothesised that daily supplementation with B vitamins would reduce total homocysteine by a quarter to a third (eg, by 3–4 µmol/L, from about 12 µmol/L to 8–9 µmol/L) and reduce the relative risk of the composite endpoint of stroke, myocardial infarction, or vascular death by 15%.

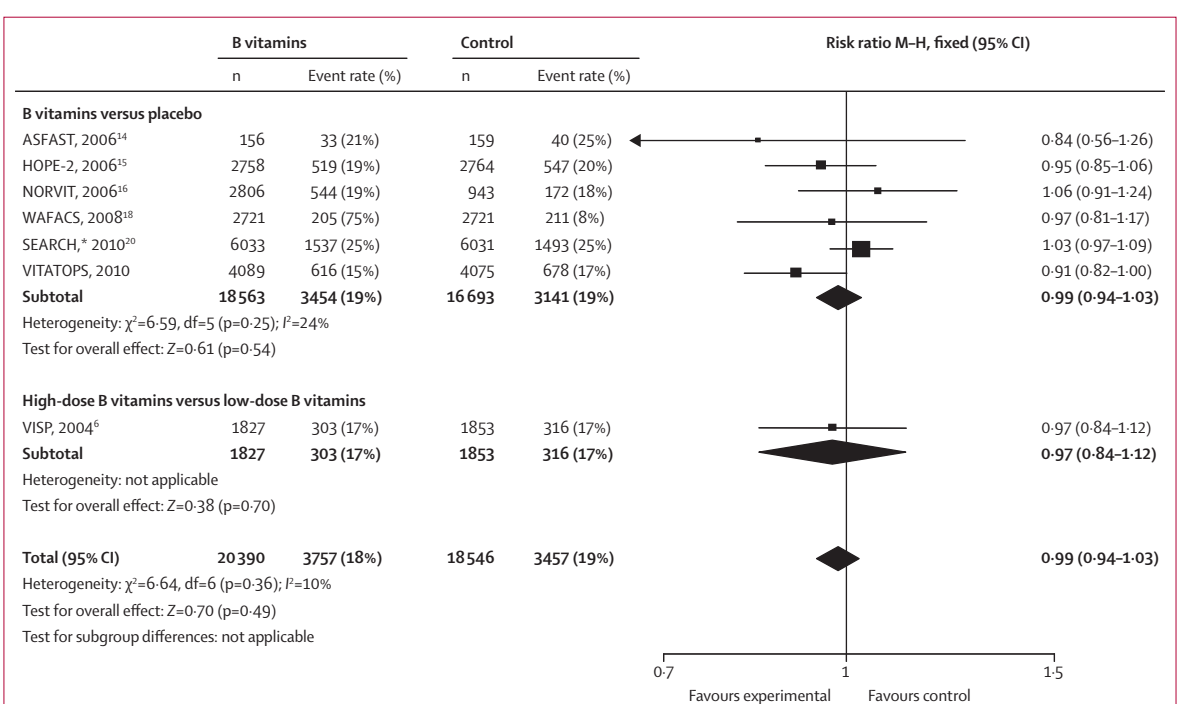

Figure 4: **Effects of treatment with B vitamins on the composite of non-fatal stroke, non-fatal myocardial infarction, or death due to vascular causes**
All trials were looking at first stroke, with the exception of the VISP trial and the VITATOPS trial, which included patients with a previous stroke. M-H=Mantel-Haenszel. *Data are for major vascular events as defined by the composite of stroke, coronary events, vascular death, and revascularisation procedures.

Estimates from meta-analyses—which were published after the design of this trial—of prospective observational studies and genotype-disease association studies suggested that lowering total homocysteine by 3 μmol/L would reduce the relative risk of stroke by about 24% (15–33%) and myocardial infarction by 16% (11–20%).[3,4]

Of the 1164 patients who volunteered to have their total homocysteine measured at final follow-up, patients in the B vitamins group had a similar reduction in total homocysteine compared with placebo (3·8 μmol/L, 95% CI 3·1–4·4 μmol/L) to that suggested in our hypothesis. The homocysteine-lowering effect of the B vitamins was consistent among different ethnic groups.[35,36]

The annual rate of primary outcomes among patients assigned to placebo was lower (4·8% per year) than expected (8·0% per year), but after prolonged recruitment and follow-up (28 179 patient-years) the number of primary outcome events (n=1294) was sufficient for the trial to be adequately powered to identify or exclude (with 95% confidence) a 15% reduction in relative risk of the primary outcome with B vitamins compared with placebo. However, we reported only a 9% reduction in the RR of the primary outcome with B vitamins compared with placebo. The 95% CIs suggest that B vitamins might reduce the risk of the primary outcome by as much as 18% or as little as 0% compared with placebo. Therefore, our findings do not definitively confirm that supplementation with B vitamins has a clinically significant beneficial effect on major vascular events.

Results from our subgroup analysis suggest that supplementation with B vitamins might reduce the risk of stroke, myocardial infarction, or vascular death in patients with symptomatic small vessel disease of the brain causing lacunar infarction or intracerebral haemorrhage. This reduction has also been suggested by other investigators who reported that homocysteine is a risk factor for cerebral small vessel disease.[28,29] If validated, this finding could explain any apparent differential effect

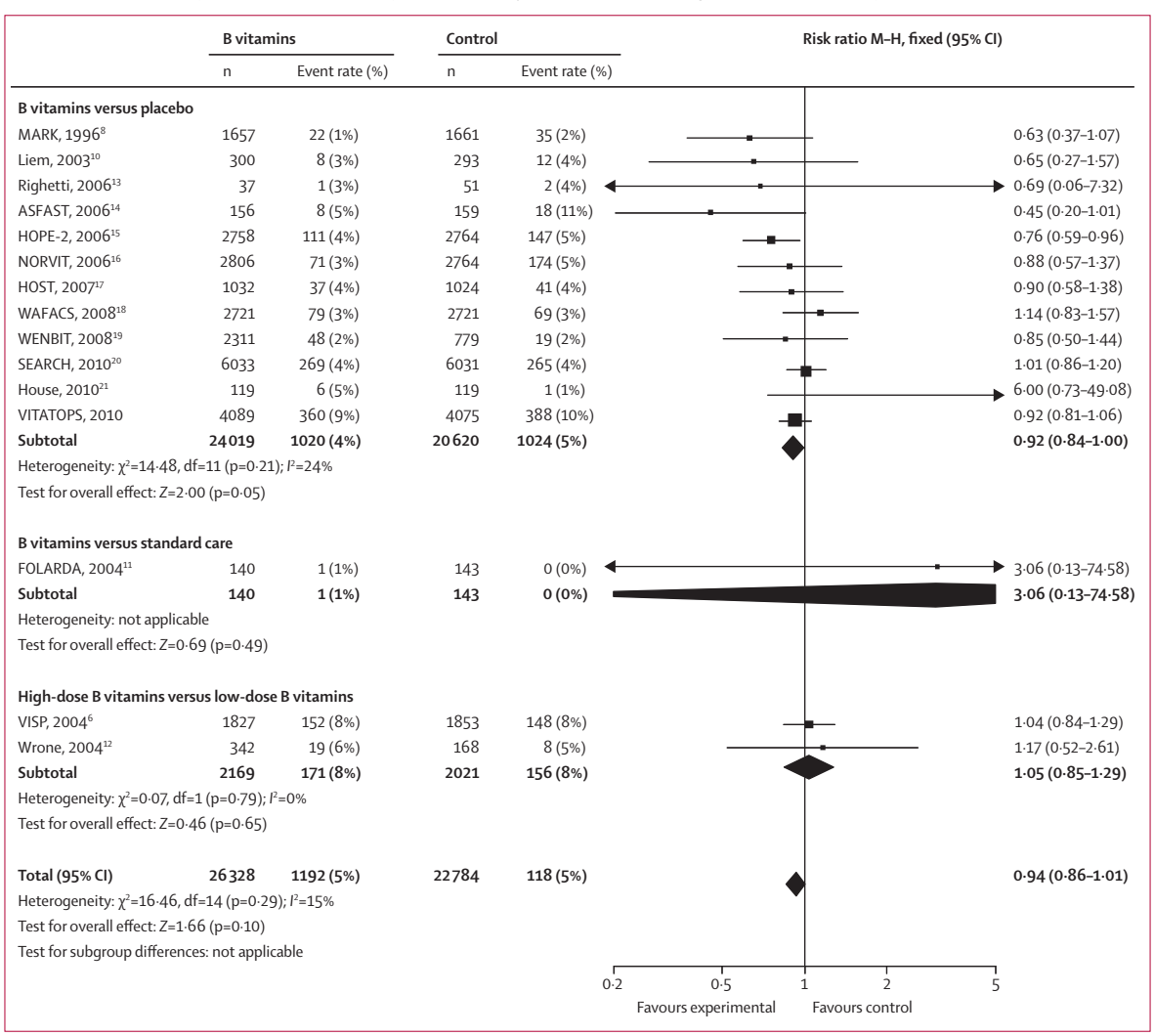

***Figure 5*: Effects of treatment with B vitamins on stroke**
All trials were looking at first stroke, with the exception of the VISP trial and the VITATOPS trial, which included patients with a previous stroke. M-H=Mantel-Haenszel.

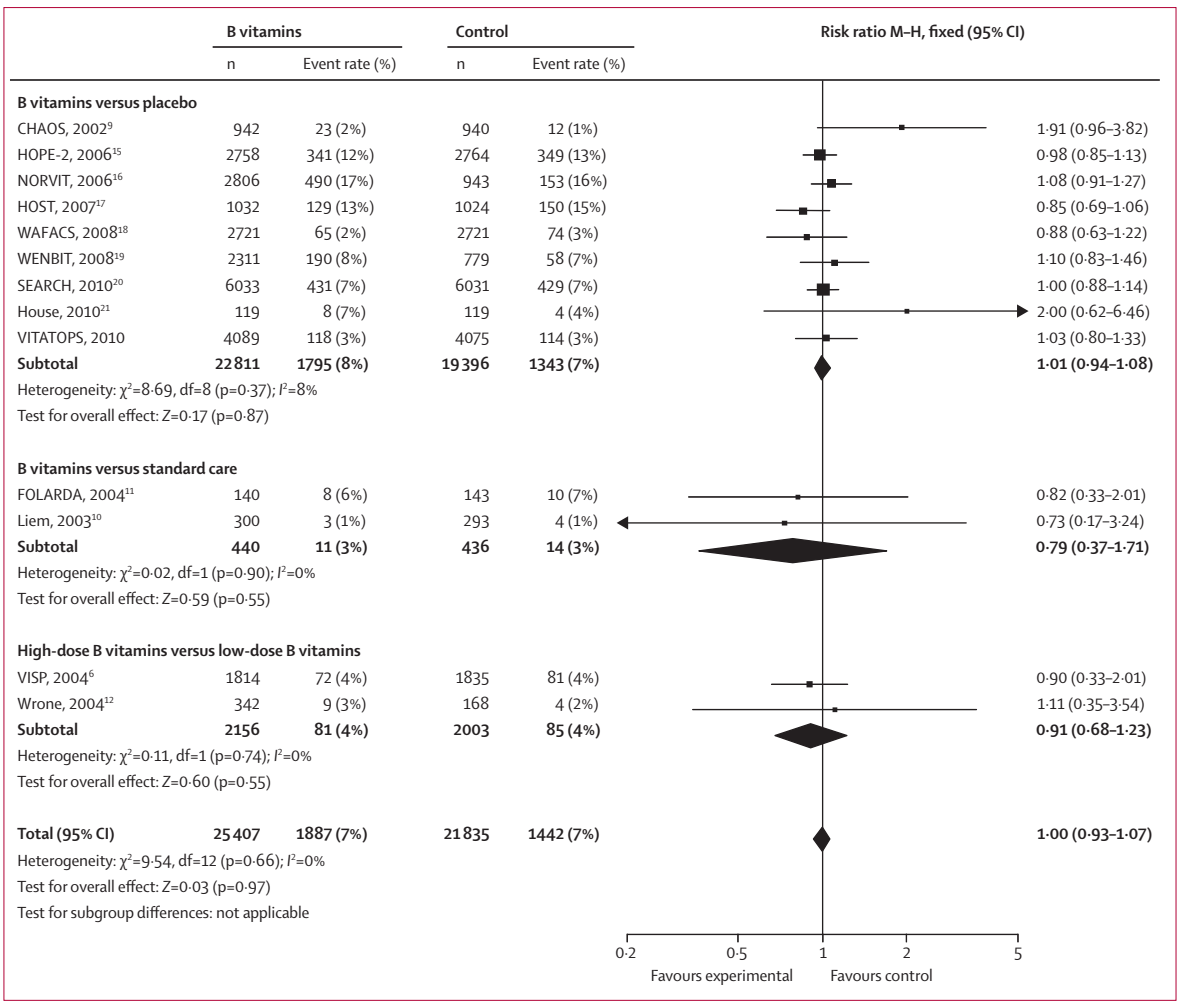

Figure 6: **Effects of treatment with B vitamins on myocardial infarction**
M-H=Mantel-Haenszel.

of homocysteine lowering on small vessel ischaemic stroke compared with large artery ischaemic stroke and myocardial infarction.

The main limitations of our trial, which could introduce bias, were incomplete adherence to trial drugs and incomplete follow-up. The high, yet similar, rates of non-adherence in each treatment group mean that any true treatment differences between the two groups would have been minimised, thus biasing the results to the null. Because of the high, yet similar, rates of loss to follow-up in each treatment group, small differences in event rates among patients lost to follow-up could have markedly affected the results of the trial. If we assume an absence of treatment effect of B vitamins among patients who were lost to follow-up and impute identical primary outcome event rates in each treatment group for those who were lost to follow-up, the relative risk for the primary outcome event would have been 0·92 (95% CI 0·83–1·01; p=0·08). If the primary outcome event rates of those lost to follow-up were consistent with the overall trial population, the relative risk for the primary event would have been 0·90 (95% CI 0·82–0·99; p=0·04). We found no evidence of a variation in treatment effect among centres in the random effects (frailty) model. If we exclude the three centres that accounted for 56% of the loss to follow-up, the results are similar to those of the whole trial population. The results of our on-treatment analysis were also consistent with our primary analysis, but they had less statistical power.

Another potential limitation of our trial is that the median duration of adherence to treatment was 2·8 years and the median duration of follow-up was 3·4 years, which might not have been long enough to adequately identify or exclude any long-term effects of B vitamins.

To minimise random error, we added our data to other randomised controlled trials of homocysteine-lowering therapy in patients with or without pre-existing cardiovascular disease (figures 4–6).[6,8–22] The updated meta-analysis suggests that B vitamins are not significantly more effective than control treatments in reducing the

Research in context

Systematic review

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (issue 1, 2010), Medline (1950–2010), Embase (1988–2010), ISI Web of Science (1993–2010), and the Cochrane Stroke Group Specialised Register (2010). We also hand-searched relevant journals and the reference lists of included papers. We included randomised clinical trials assessing the effects of B vitamins (folic acid, vitamin B12, and vitamin B6) in lowering blood concentrations of homocysteine and preventing stroke and other major cardiovascular events. We assessed papers with stroke, myocardial infarction, and death attributable to vascular causes as the primary outcomes.

Interpretation

The VITATOPS trial shows, for the first time, that B vitamins are safe but not significantly more effective than placebo in reducing the risk of major vascular events among patients with a history of recent stroke or transient ischaemic attack. These results are consistent with trials of B vitamins in other patient populations.

risk of the composite of stroke, myocardial infarction, or vascular death (0·99, CI 0·94–1·03, p=0·49; figure 4); stroke (RR 0·94, 95% CI 0·86–1·01; p=0·10; figure 5); or myocardial infarction (1·00, 0·93–1·07; p=0·97; figure 6).

A planned meta-analysis of individual data from all previous, and three ongoing, randomised controlled trials of B vitamins will provide more reliable estimates of the long-term effects of B vitamins in the prevention of stroke and other major vascular events among patients with stroke or transient ischaemic attack, particularly when caused by symptomatic cerebral small vessel disease (deep intracerebral haemorrhage and lacunar infarction).[37–40]

Contributors

GJH and JWE designed the study and directed the trial. GJH obtained funding in Australia, recruited and followed up patients, and wrote the first and final drafts of the manuscript. CC obtained funding in Singapore, recruited and followed up patients and was the national coordinator of the trial in Singapore. JWE obtained funding in Australia. KRL obtained funding in the UK, recruited and followed up patients, and was the national coordinator of the trial in the UK. CC, JWE, and KRL contributed to each draft of the manuscript. QY did the statistical analyses.

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Conflicts of interest

GJH has received payments for serving as a member of the executive committees of the ROCKET-AF (Johnson and Johnson), AMADEUS (Sanofi-Aventis), and BOREALIS (Sanofi-Aventis) trials; the steering committee of the TRA-2P TIMI 50 trial (Schering Plough); the Australian Pradaxa (dabigatran) advisory board (Boehringer Ingelheim); a working group on stroke and lipid management in Asia (Pfizer); has received honoraria for speaking at scientific symposia sponsored by Sanofi-Aventis and Pfizer Australia; and has received travel and accommodation expenses from Sanofi-Aventis. JWE has received consulting fees and honoraria for lecturing at sponsored scientific symposia from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Astra, and Novartis, and has received payment for lectures from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and Astra. JWE's institute has received grants from Bristol-Myers Squibb. CC has received payments for serving as national coordinator of the PERFORM (Servier) trial, on the data monitoring committee of the DU176B-C-J226 (Dai-Ichi) trial, as adviser to the ImpACT-24 (Brainsgate) trial, and for being part of a working group on stroke and lipid management in Asia (Pfizer), and has received travel and accommodation expenses from Moleac to attend the European Stroke Congress. KRL has received consultancy payments for serving on data monitoring committees for Lundbeck (DIAS-3,4), Boehringer Ingelheim (ECASS-3), Ferrer (ICTUS), Photothera (NEST-3), Archemix, Astellas, Mitsubishi, and Talecris, the trial endpoint committee for GlaxoSmithKline (RECORD), and the trial steering committees for D-Pharm (MACSI) and Servier (PERFORM) and has received honoraria for lectures at scientific symposia sponsored by Ferrer, Boehringer Ingelheim, and Sanofi-Aventis. QY has no conflicts of interest.

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