**Homocysteine-lowering therapy: a role in stroke prevention?**

J David Spence

On the basis of the results of several recent clinical trials, many researchers have concluded that vitamin therapy designed to lower total homocysteine concentrations is not effective in reducing the risk of cardiovascular events. However, whereas almost all myocardial infarctions are due to plaque rupture, stroke has many more pathophysiological mechanisms, and thrombosis—which is increased by raised total homocysteine concentrations—has an important role in many of these processes. Thus, stroke and myocardial infarction could respond differently to vitamin therapy. A detailed assessment of the results of the recent HOPE-2 trial and a reanalysis of the VISP trial restricted to patients capable of responding to vitamin therapy suggest that higher doses of vitamin B12 and perhaps new approaches to lowering total homocysteine besides routine vitamin therapy with folate, vitamin B6, and vitamin B12 could reduce the risk of stroke. Thus, therapy to lower homocysteine could still help to prevent stroke, if not other vascular outcomes.

**Introduction**

Unravelling the risk factors for stroke remains an important challenge. An increased understanding of the underlying mechanisms will help us to identify ways in which we can reduce the incidence of stroke. One potential risk factor is increased plasma concentrations of homocysteine, a sulphur-containing amino acid that is formed during methionine metabolism and can be regulated by the vitamins folic acid, B6, and B12. The vascular effects of raised homocysteine concentrations were first noted in 1962 in patients with the hereditary metabolic disorder homocystinuria and very high concentrations of total homocysteine (the sum of homocysteine, homocysteine–homocysteine, and homocysteine–cysteine disulfide), resulting from a homozygous deficiency of cystathionine synthase. In 1969, McCully suggested that even moderate increases of total homocysteine could accelerate atherosclerosis. Later, a third of patients with premature atherosclerosis were reported to have raised concentrations of total homocysteine and 42% of patients with premature vascular disease had hyperhomocysteinaemia, both of which were attributed to heterozygous homocysteineuria. Many causes of raised total homocysteine have since become apparent: about a dozen genetic defects, renal failure, vitamin deficiencies, increasing age, and a number of drugs including methotrexate, anti-convulsants, proton pump inhibitors, and fibrates are associated with increases in total homocysteine. Moreover, animal models and studies of the biochemical pathways involving homocysteine suggest that increases in total homocysteine could aggravate vascular disease and support a causal role for total homocysteine in vascular disease. A high total homocysteine concentration has been shown in large cohort studies to be an independent, graded predictor of cardiovascular events, including cerebral infarction, myocardial infarction, and cardiovascular death. However, recent clinical trials have been interpreted as showing that homocysteine is not causal in vascular disease because vitamin therapy to reduce homocysteine concentrations did not reduce the incidence of myocardial infarction or stroke.

Here, I summarise and assess pathophysiological, genetic, and clinical evidence that homocysteine is involved in vascular disease, especially with respect to cerebral infarction. Moreover, a closer look at the results from recent clinical trials with respect to stroke calls into question the initial interpretation that homocysteine is not causal in vascular disease and suggests that there could indeed be an effect of vitamin therapy to lower total homocysteine, at least for cerebral infarction. This reassessment of the evidence from clinical trials raises the important issues of variations in individual responses to vitamin therapy and the need for higher doses of vitamin B12 than have been used in clinical trials to date, especially since stroke mainly affects elderly individuals, who are more likely to be deficient in vitamin B12.

**Genetic risk**

Support for a causal role for total homocysteine in the risk of stroke has come from genetic approaches. Perhaps the most common single nucleotide polymorphism leading to increased concentrations of total homocysteine is the C→T mutation of the methylene tetrahydrofolate reductase (MTHFR) gene. Casas and colleagues did two large-scale meta-analyses to assess the link between homocysteine and stroke. In the first, they aimed to determine the extent to which the MTHFR C677T polymorphism is associated with homocysteine concentration, and in the second they investigated the effect of this polymorphism on stroke. The expected odds ratio for stroke corresponding to this difference, on the basis of previous observational studies, was 1·20 (1·10–1·31). In their genetic meta-analysis (n=13 928), Casas and colleagues reported an odds ratio for stroke of 1·26 (1·14–1·40) for TT versus CC homozygotes, similar to the expected odds ratio (p=0·29). Because this polymorphism would be randomly allocated, there should not be residual confounding or reverse-causality bias in the relation between stroke and homocysteine. Therefore, the consistency in the odds ratios between the two meta-analyses indicates that there is a causal relation between increased homocysteine concentrations and stroke.

In support of this finding, Cronin and colleagues found a dose-dependent relation between the MTHFR
677T allele and stroke: among 14 870 individuals, the odds ratio for risk of stroke or transient ischaemic attack associated with the T genotype was 1.17 (95% CI 1.09–1.26) and that for the TT genotype was 1.37 (95% CI 1.15–1.64). Perhaps because there are many other causes of raised total homocysteine besides a C→T mutation of MTHFR, my colleagues and I found that total homocysteine, but not MTHFR, was associated with increased carotid total plaque area. However, from these genetic studies, a causal relation between total homocysteine and stroke does seem possible.

Pathophysiological mechanisms
There are many mechanisms by which increased total homocysteine could contribute to vascular disease. The strongest evidence for this link comes from studies of animal models and indicates that the principal mechanisms involve impaired endothelial function, increased oxidative stress, alterations of lipid metabolism, and induction of thrombosis.

Raised plasma total homocysteine concentrations have been associated with increased coagulation of the blood, increased cholesterol synthesis, increased oxidative stress, reduced synthesis of apolipoprotein A1 leading to reduced concentrations of high density lipoprotein, effects on lipoprotein(a), induction of calcium as a second messenger in smooth muscle cells, upregulated adhesion molecules, and several mechanisms that impair endothelial function, including endothelial cell apoptosis, consumption of nitric oxide, increased asymmetric dimethylarginine, and increased release of endothelin. Raised total homocysteine concentrations seem to be causal in animal models of atherosclerosis; a recent study showed that increased total homocysteine interacted with hypercholesterolaemia in accelerating plaque development, impairing endothelial function and promoting thrombosis. This finding is supported by studies of patients with hyperhomocystaemia, who have impaired endothelial function.

In addition to mechanisms relating to increased circulating concentrations of total homocysteine, important intracellular mechanisms by which total homocysteine can adversely affect atherosclerosis have become apparent, including stress of the endoplasmic reticulum. Moreover, a novel mechanism by which homocysteine accelerates vascular disease was recently reported by Barbato and colleagues: L-homocysteine targets intracellular metallothionein by forming a mixed-disulfide conjugate; loss of function occurs after homocysteinylatation. This loss of function leads to disruption of zinc and redox homeostasis, which accelerates vascular disease. Colgan and Austin suggest that intracellular targets of homocysteine could be the underlying cause of endothelial cell dysfunction. Thus, there could be many mechanisms by which raised total homocysteine would adversely affect vascular disease, and stroke in particular.

Raised homocysteine and cerebral infarction
Whereas almost all myocardial infarctions are due to plaque rupture in a coronary artery, with in-situ thrombosis that is secondary to the plaque rupture, there are many more mechanisms that lead to cerebral infarction. Indeed, cerebral infarction is rarely due to carotid artery occlusion. A major difference between the causal factors for myocardial infarction and stroke is the richer collateral circulation to the brain. Whereas complete occlusion of a left main coronary artery would rarely be asymptomatic, it is common for carotid occlusion to cause no symptoms, or minor symptoms, because the middle cerebral artery territory distal to the occlusion is supplied by collaterals from the vertebrobasilar system via the posterior communicating artery, and from the opposite carotid, via the anterior communicating artery. Moreover, a substantial proportion of strokes (including cardioembolic strokes and those due to cortical venous thrombosis) are related to thrombotic processes, which can be associated with raised total homocysteine. Risk of stroke in atrial fibrillation is increased more than four-fold by high concentrations of total homocysteine (figure 1). Increased concentrations of total homocysteine are therefore likely to be more important for cerebral infarction than for myocardial infarction.

Homocysteine as a marker of vascular disease
Some researchers suggest that rather than having a causal role in vascular disease, homocysteine might be just a marker of disease. This hypothesis is based on an apparent rise in homocysteine concentrations between
samples obtained after admission to hospital with stroke and samples obtained after discharge from hospital. However, this increase is more likely to be explained by the timing of blood sample collection after acute stroke. The apparent rise in total homocysteine after an acute stroke\(^{71}\) probably indicates an initial decline in total homocysteine concentration due to haemodilution when the patient becomes recumbent, returning to premorbid levels as the patient is mobilised. This is analogous to the findings of Campbell and colleagues\(^ {70,71}\), who showed that diuretic therapy and standing, by causing haemoconcentration, increase the plasma concentrations of cholesterol. Many other blood analyses would be similarly increased in concentration by haemoconcentration. In view of all the evidence presented in this review, it seems unlikely that total homocysteine would be only a marker of disease.

**Vitamin therapy and surrogate outcomes**

Studies of the effects of vitamin therapy on surrogate outcomes such as endothelial function or carotid plaque progression lend support to the notion that homocysteine concentrations are linked to risk of vascular events. Lowering of homocysteine by vitamin\(^{50}\) or acetylcysteine therapy improves endothelial function in patients with vascular disease or with renal failure.\(^ {70–74}\) In patients whose carotid plaque was progressing despite treatment of traditional risk factors, my colleagues and I showed that vitamin therapy halted the progression of carotid plaque,\(^ {71}\) both for patients with total homocysteine below and for those with concentrations above 14 µmol/L, which was regarded as abnormal at the time of the study.\(^ {73}\) Vermeulen and colleagues\(^ {72}\) showed a reduction of myocardial ischaemia detected by ECG stress tests in a trial of vitamin therapy for homocysteine in patients with peripheral vascular disease. In renal transplant patients, Marcucci and colleagues\(^ {73}\) showed that vitamin therapy for homocysteine slowed the progression of carotid intima–media thickness.

**Large-scale clinical studies**

Scepticism about the role of homocysteine in vascular events is understandable given the mixed results of clinical studies and the results of several randomised controlled trials in which vitamin therapy to reduce homocysteine concentrations was not associated with a reduction in the incidence of myocardial infarction or stroke. Although clinical trials undoubtedly rank at the top of the hierarchy of evidence, it must be understood that they are a blunt instrument, and interpretation of their results requires an understanding of the mechanisms of the disease under study. Here, I review large-scale clinical studies, including recent randomised clinical trials, designed to assess the effects of homocysteine-lowering therapy on vascular events, and evaluate the evidence particularly with respect to cerebral infarction.

**Epidemiological studies**

In 1997, a case-control study and a large prospective study in patients with vascular disease showed that total homocysteine, even at low concentrations, was a strong, graded, and independent predictor of cardiovascular events.\(^ {21,22}\) Total homocysteine concentrations above 10–2 µmol/L were associated with a doubling of the risk of myocardial infarction and stroke\(^ {72}\) and levels above 20 µmol/L with a nine-fold increase in risk.\(^ {22}\) compared with concentrations below 9 µmol/L. The Hordaland Homocysteine study,\(^ {73}\) a prospective population-based study in more than 18 000 men and women aged 40–67 years at baseline and followed-up for 5 years, showed that individuals with raised total homocysteine concentrations had increased risk of cardiovascular morbidity, cardiovascular and non-cardiovascular mortality, and were more likely to experience depression and cognitive deficit compared with those with normal total homocysteine concentrations. These relations were concentration dependent. During 4 years of follow-up, mortality among high-risk participants who had a history of previous cardiovascular disease was 2.9% in those with total homocysteine less than 9 µmol/L, compared with 21% in those with a total homocysteine concentration of 20 µmol/L or more.\(^ {74}\)

**Coronary angioplasty trials**

Coronary angioplasty with follow-up angiography affords an opportunity to assess directly the effect of homocysteine on the coronary arteries. Ortolani and colleagues\(^ {75}\) found that, among patients with unstable angina undergoing stenting, those in the top quartile of total homocysteine concentrations (>17 µmol/L) had similar rates of revascularisation similar to the other three quartiles combined (11.2% vs 13.2%, p=0.90), but higher total (13.3% vs 0.7%, p=0.001) and cardiac (6.7% vs 0%, p=0.01) mortality. Two randomised controlled trials of vitamin therapy in coronary angioplasty patients gave contrasting results. The aim of both trials was to determine, among patients who had undergone successful coronary angioplasty, whether vitamin therapy for homocysteine would reduce restenosis. Schnyder and colleagues\(^ {76}\) randomly assigned 553 such patients to receive either a combination of folic acid (1 mg), vitamin B12 (400 µg), and pyridoxine (10 mg) daily for 6 months, with outcomes assessed at 6 months and 1 year, or placebo. Vitamin therapy reduced restenosis\(^ {77}\) and, in a follow-up study, vascular events.\(^ {78}\) After 11 months, the composite outcome of death, non-fatal myocardial infarction, and revascularisation occurred with a frequency of 15.4% in those on vitamin therapy compared with 22.8% in those on placebo (RR 0.68, 95% CI 0.48–0.96; p=0.03). Lange and colleagues\(^ {79}\) randomly assigned 636 such patients to receive either a combination of folate (1 mg), vitamin B6 (5 mg), and vitamin B12 (60 µg) for 6 months—with angiographic outcomes assessed at 6 months—or placebo; after
6 months, there was greater restenosis in the group that was taking the vitamin therapy. The discrepancy in the results between these two trials could have been caused by the dose of vitamin B12, which was nearly ten times higher in Schnyder and colleagues’ study.

**Norwegian Vitamin Trial (NORVIT)**

The Norwegian Vitamin Trial\(^5\) was done in 3749 patients who had an acute myocardial infarction within the 7 days before randomisation. The purpose of the study was to determine whether vitamin therapy for homocysteine would reduce vascular events, and to attempt to determine which component(s) of vitamin therapy were most important. Patients were randomly assigned, in a 2×2 factorial design, to receive one of the following four daily treatments: 0·8 mg folic acid, 400 μg vitamin B12, and 40 mg vitamin B6; 0·8 mg folic acid and 400 μg vitamin B12; 40 mg vitamin B6; or placebo. The primary endpoint during a median follow-up of 40 months was a composite of recurrent myocardial infarction, stroke, and sudden death attributed to coronary artery disease. There was no reduction of cardiovascular events in any of the study groups, and the authors suggested that there could have even been a harmful—although not significant—effect of vitamin therapy.

However, there are some concerns about the design and inclusion criteria for NORVIT. The factorial design dictated that the key comparison (between placebo and folate, vitamin B6, and vitamin B12) was limited to a small part of the sample. Furthermore, an inordinate proportion of patients who were randomised were smokers (46%), which might explain why the rate of accumulation of events was also very steep (about twice as rapid as in the Vitamin Intervention for Stroke Prevention (VISP) trial, in which only about 16% of participants receiving low-dose vitamins and about 18% of those receiving high-dose vitamins were smokers), raising questions about the underlying causes of the events.

**HOPE-2**

In the Heart Outcomes Prevention Evaluation 2 (HOPE-2) study,\(^6\) 5522 patients aged 55 years or older with vascular disease or diabetes were assigned at random to receive daily treatment with placebo or with the combination of 2·5 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12, for an average of 5 years. The aim of the study was to determine whether vitamin therapy for homocysteine reduced the risk of vascular events. There was no reduction in the primary outcome, a composite of death from cardiovascular causes, myocardial infarction, and stroke. However, there was a significant reduction in stroke (relative risk 0·75; 95% CI 0·59–0·97; p=0·03).

The investigators attributed this finding to chance, because they did not think that any biological reason would account for a difference in response of stroke to vitamin therapy, compared with other cardiovascular endpoints. However, a biological difference between stroke and cardiac events is entirely to be expected. Indeed, the Homocysteine Studies Collaboration predicted almost twice the effect on stroke than on myocardial infarction: a 19% reduction of stroke with a 3 μmol/L reduction of total homocysteine versus an 11% reduction of coronary events.\(^7\) An accompanying commentary by Refsum and Smith\(^8\) shows a steady divergence in events between the participants assigned to vitamin therapy compared with those on placebo, indicating that the difference is very unlikely to be due to chance alone (figure 2). If vitamin therapy had no effect on stroke risk, the lines should cross repeatedly during the course of the study, or should remain close together; the continued divergence of risk between the two treatment groups strongly indicates that the difference was not due to chance. Furthermore, the magnitude of stroke reduction in HOPE-2 was consistent with previous meta-analyses\(^9,10\) that predicted a 19–24% decrease of stroke with the reduction of total homocysteine seen in HOPE-2. Thus, the significant reduction of stroke with vitamin therapy in the HOPE-2 trial supports the hypothesis that vitamin therapy reduces risk of stroke.

**VISP**

In the VISP trial,\(^11\) 3680 patients who had experienced a non-disabling ischaemic stroke were randomly assigned to receive multivitamin tablets that contained the usual recommended daily intake of other vitamins, with either a low dose or a high dose of folate, vitamin B6, and vitamin B12. The aim of the study was to determine whether vitamin therapy for homocysteine reduced the risk of recurrent stroke and of coronary events or vascular
death. The low-dose arm received the recommended daily intake of vitamin B12 (6 μg), with folate (20 μg), and vitamin B6 (200 μg) daily. The high-dose arm received folate (2.5 mg), vitamin B6 (25 mg), and vitamin B12 (400 μg). The primary intention-to-treat analysis showed no reduction of stroke, coronary events, or vascular death.

There were, however, several issues that could have confounded this analysis. The low-dose arm received the recommended daily intake of vitamin B12, and the dose of vitamin B12 in the high-dose group turns out, in retrospect, to have been too low: a dose-response study in elderly individuals with serum concentrations of vitamin B12 below 212 pmol/L (still within the normal range) showed that 1 mg daily would have been more appropriate. Furthermore, monthly injections of vitamin B12 were given to patients in either arm of the study who had low serum concentrations of vitamin B12, thus negating the effect of vitamin B12 in the very participants who would have benefited most from it. To make matters worse, the introduction of folate fortification of grain products in North America coincided with the initiation of the study, thus negating the effect of the folate in the high-dose arm of the study.

My colleagues and I did an efficacy analysis from which patients who could not benefit from the vitamin intervention were excluded—ie, patients with low concentrations of vitamin B12 (who would have received injections of the vitamin), and patients with renal failure, who are known not to be as responsive to vitamin therapy. In this remaining population of 2155 participants, high-dose vitamin therapy significantly reduced stroke, coronary events, and death. Stratification by entry concentrations of vitamin B12—above and below the median concentration of 322 pmol/L—made it clear that the ability to absorb vitamin B12 was the key determinant of response to vitamin therapy. Whereas the analysis comparing high-dose versus low-dose vitamin therapy showed only a 20% reduction of events (p=0.049), the stratified analysis gave a reduction of events significant at the level of p=0.02 (log-rank test in the Kaplan-Meier analysis) for all groups (figure 3). Patients able to absorb vitamin B12 who entered the study with a serum B12 concentration above the median and who received high-dose vitamins had an event rate of only 12%, compared with 18% for the patients whose B12 absorption was less effective with entry serum concentrations of vitamin B12 below the median who received low-dose vitamins. In other words, events were reduced by a third in patients capable of absorbing vitamin B12 who received high-dose vitamins. These findings suggest that, in future, we need to use higher doses of vitamin B12 and, as suggested by Loscalzo, we need to find other means to lower homocysteine for those who are unable to respond to vitamin therapy.

Meta-analysis of clinical trials
A meta-analysis of randomised controlled trials designed to assess the effects of folic acid supplementation on cardiovascular events did not show any benefit of folate therapy for vascular disease. However, the study did suggest a better effect of vitamin therapy for stroke: although not significant, the relative risk of stroke with vitamin therapy was 0.86 (95% CI 0.71–1.04), compared with 1.04 (0.92–1.17) for myocardial infarction, lending support to the possibility that stroke might be more closely related to total homocysteine than is myocardial infarction.

Furthermore, a recent meta-analysis of eight randomised trials of so-called folate therapy, in which stroke was one of the endpoints, showed a significant 18% reduction of stroke (relative risk 0.82, 95% CI 0.68–1.0). There were greater effects in studies of longer duration and with greater reductions of total homocysteine.

Unrecognised importance of vitamin B12
Because stroke is more steeply related to age than is myocardial infarction, the issue of vitamin B12 deficiency, which is much more common in elderly individuals, could have an important role in the differential effect of vitamin therapy on stroke versus myocardial infarction. Indeed, patients in VISP and HOPE-2, where stroke reduction was found with vitamin therapy, were older than those in the two angioplasty trials or in NORVIT. Dietary factors are also crucial in determining circulating concentrations of total homocysteine.

Vitamin B12 deficiency in elderly people
Deficiency of vitamin B12 in elderly individuals is far more common than most physicians suppose, when they assume that concentrations of vitamin B12 within
the normal range are adequate. This is an important problem, because in addition to the increase of total homocysteine that results from vitamin B12 deficiency, there are neurological consequences including neuropathy, subacute combined degeneration of the spinal cord, and dementia. Measurement of serum concentrations of vitamin B12 is not sufficient to make a diagnosis of vitamin B12 deficiency; measurement of holotranscobalamin is much more sensitive, but is not widely available. The normal range of serum concentrations of vitamin B12 is typically 160–600 pmol/L. By definition, only 2.5% of the population are below the statistically normal concentration of serum vitamin B12, but metabolically adequate concentrations of serum vitamin B12 are defined by the ability to suppress methylmalonic acid below 271 pmol/L, or in folate-replete individuals (which now essentially means over 98% of people living where folate fortification is in place), to suppress total homocysteine below 14 μmol/L. By these definitions, 20% of elderly individuals are vitamin B12 deficient. In the population of vascular patients studied by Robertson and colleagues, low serum vitamin B12 was strongly associated with higher total homocysteine and with more carotid plaque. An analysis using the above definitions for vitamin B12 deficiency showed that, among these vascular patients, metabolic vitamin B12 deficiency was present in 12% of patients below age 50 years, 13% of those aged 50–71 years, and 30% of those above age 71 years. Quinlivan and colleagues also found that, in folate-replete patients, vitamin B12 was the key determinant of total homocysteine concentrations. Thus, unrecognised vitamin B12 deficiency—and failure to use adequate doses of vitamin B12 in clinical trials of vitamin therapy for homocysteine—could be partly (or largely) responsible for the failure of folate therapy to reduce cardiovascular risk.

**Dietary factors**

Strict vegetarians are more likely to be deficient in vitamin B12 than are non-vegetarians because it is obtained mostly from meat. Dietary folate and betaine are obtained mainly from plants, so people who consume little fruit or vegetables could be deficient in these nutrients. In India, where many individuals are vegetarian and cooking methods destroy folate by prolonged heating at high temperatures, both vitamin B12 and folate deficiency are common. Asian Indians in the USA are also more likely to have hyperhomocysteinaemia—compared with four other ethnic groups—mainly as a result of vitamin B12 deficiency. Dietary intake of nutrients involved in homocysteine metabolism are therefore important.

**Other therapies for lowering homocysteine**

Although routine therapy with folate, vitamin B6, and vitamin B12 is effective in lowering concentrations of total homocysteine in most patients, some patients have high total homocysteine despite vitamin therapy. Reasons for this lack of effect include renal failure and probably genetically based differences in homocysteine metabolism. Such patients can benefit from addition of betaine (trimethylglycine) or choline (in the form of phosphatidylcholine), which affect other metabolic pathways for the removal of vitamin B12.

Treatment to lower concentrations of total homocysteine can be particularly difficult in patients with impairment of renal function. Homocysteine and the other molecular species that make up total homocysteine are highly protein-bound; thus, they are not well excreted in the urine, nor well removed by dialysis. One approach to this problem is to increase the intensity of dialysis; overnight daily dialysis virtually normalises concentrations of total homocysteine. Other options include acetylcysteine therapy, which shows only modest success in reducing concentrations of total homocysteine, but improves endothelial function in dialysis patients. Likewise, dimercaptosuccinic acid does not usually reduce concentrations of total homocysteine in dialysis patients, although it had substantial effects in some patients. Another approach that can be used in patients not yet on dialysis is to remove total homocysteine from plasma proteins by binding it to thiols. Urquhart and colleagues have developed an in-vitro thiol exchange assay that shows that mesna—a thiol-containing drug normally used to prevent ifosfamide-induced haemorrhagic cystitis—and captopril have a greater effect than acetylcysteine, and dimercaptosuccinic acid had little effect on removing total homocysteine from proteins. My colleagues and I have recently shown that a single dose of mesna substantially lowers total homocysteine in dialysis patients.

**Conclusions**

The results of three randomised controlled trials of vitamin therapy for reduction of vascular events, all of which failed to show benefit of vitamin therapy for their primary outcome, have justifiably caused many to conclude that vitamin therapy to lower homocysteine is ineffective in preventing vascular disease. Several recent reviews reflect this doubt, which amounts almost to a consensus. Although recommendation of widespread homocysteine-lowering therapy for the reduction of myocardial infarction might be premature, there are important differences between myocardial infarction and cerebral infarction that suggest that lowering homocysteine, by reducing thrombosis and thereby embolic events, could be more effective for prevention of cerebral infarction. The relation between homocysteine and vascular events is supported by biologically plausible mechanisms including impaired endothelial function, oxidative stress, increased thrombosis, and intracellular mechanisms. Genetic studies provide evidence supporting causality, as do
animal studies and human studies of effects of vitamin therapy on carotid plaque and intima-media thickness.

Importantly, a reassessment of the results of the HOPE-2 trial, supported by an efficacy analysis of the VISP trial, suggest that vitamin therapy to lower homocysteine could indeed reduce the risk of stroke, if not other vascular outcomes. The results of the Vitamin to Prevent Stroke (VITATOPS) study, a large multicentre international clinical trial of secondary stroke prevention with folate, vitamin B6, and vitamin B12, should help to clarify the question of whether vitamin therapy to lower total homocysteine reduces the risk of stroke. As shown by the efficacy analysis of the VISP trial, higher doses of vitamin B12 might be needed to reduce total homocysteine effectively. Moreover, folate therapy by itself, especially where folate fortification of grain products is in effect, is not necessarily beneficial for vascular disease, and future work should aim to identify additional ways of lowering total homocysteine to further improve prevention of vascular disease.

Conflicts of interest
I have received supplies of vitamin and matching placebo for a clinical trial funded by the Canadian Institutes of Health Research, and speaker's fees and consulting fees from Pan American Laboratories, Wyeth Consumer Healthcare, and Medice Arzneimittel Pütter GmbH & Co relating to homocysteine.

References


