

# CAT Clinic

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## Can B vitamin therapy help to prevent future vascular events?

A 70-year-old man with a history of type 2 diabetes, dyslipidemia, and MI (in 2000) is admitted to the hospital after experiencing difficulty speaking and right hemiparesis upon awakening this morning. The symptoms have resolved by the time he arrives in the emergency department. The initial workup, which includes head CT, laboratory tests, and radiology and ECG evaluations, is unremarkable. The patient is admitted for observation and initiation of an expedited workup for transient ischemic attack. Your hospital has preprinted stroke admission order forms that include suggested testing for homocysteine levels. You ask yourself, “Is there any evidence that reducing homocysteine levels will help prevent further vascular events?”

### CLINICAL QUESTION

In patients with pre-existing vascular disease, does reducing elevated homocysteine levels with folate/vitamin B<sub>12</sub> treatments prevent future vascular events?

### SEARCH CRITERIA AND RESULTS

This is a question about secondary prevention and thus falls into the general category of therapy. The highest levels of evidence to answer questions about therapy are high-quality meta-analyses, systematic reviews, or large randomized controlled trials (RCTs).

A search of the medical literature is conducted using the following terms in MEDLINE 1966-current: *homocysteine OR folic acid OR folate OR vitamin B<sub>12</sub> or B vitamins AND vascular diseases OR cardio-*

*vascular diseases OR cerebrovascular disease OR stroke OR myocardial infarction.* The search is limited to *English language AND humans* and uses the saved *therapy* search hedge. This yields 849 articles. Limiting to *core clinical journals (AIM)* yields a still unmanageable 178 articles. Sometimes, limiting to AIM can miss important articles, though this was not the case in this example and the number of results was still too unwieldy. In contrast, limiting to *EBM reviews* instead of AIM yielded 18 articles and identified the most pertinent ones. In this situation, EBM reviews returned a manageable number of articles without eliminating any relevant studies, but this search tool is not available in all MEDLINE searches. Further searching of PubMed, evidence-based medicine prefiltered databases such as DARE, the Cochrane databases, Clinical Evidence, *Bandolier*, etc, failed to yield any additional articles that were more pertinent or of a higher level of evidence.

Ultimately, two recent, large RCTs that address your clinical question are found: the HOPE 2 trial<sup>1</sup> and the VISP trial.<sup>2</sup> The HOPE 2 trial is larger and more recent, and it compared folate/B vitamins with placebo, whereas the VISP trial compared different dosage strengths. The HOPE 2 trial also had a longer follow-up period. However, both provide useful information to help answer your clinical question.

### EVALUATING THE EVIDENCE

The HOPE 2 trial asked the question, “In patients with vascular disease, does lowering homocysteine with folate/B vitamins reduce the risk of major vas-

cular events?” It was a multicenter (145 centers in 13 countries with and without mandatory folate fortification) RCT, double-blind and placebo-controlled, with a mean follow-up of 5 years and only 0.7% loss to follow-up. Allocation was concealed.

The study enrolled 5,522 patients, regardless of homocysteine level, who were older than 55 years (mean, 69 years; 72% male) and had a history of coronary artery disease (CAD), cerebrovascular disease, peripheral artery disease, or diabetes with one or more risk factors for atherosclerosis. In the end, 54% had a history of MI and 9% had a history of stroke. The main exclusion criteria were planned revascularization or ingestion of more than 200 mcg folate daily already.

Patients were randomized either to placebo (n = 2,764) or to a combination of 2.5-mg folate/50-mg vitamin B<sub>6</sub>/1-mg vitamin B<sub>12</sub> taken once daily (n = 2,758). Follow-up at 5 years demonstrated that 90.8% of participants were still taking the study drug. The primary outcome was a composite endpoint of MI, stroke, or vascular-related death. Secondary outcomes included hospitalization for unstable angina, revascularization, total ischemic events (primary outcome plus hospital-

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ization for unstable angina or revascularization) and all-cause deaths.<sup>1</sup>

The mean baseline homocysteine in the final sample was 12.2  $\mu\text{mol/L}$ . In a randomly selected subgroup, the mean homocysteine level at 2 years decreased by 2.2  $\mu\text{mol/L}$  in the intervention group and increased by 1.1  $\mu\text{mol/L}$  in the placebo group. However, the groups did not differ in primary composite endpoints including total ischemic events or death from any cause. For unexplained reasons, hospitalization for unstable angina was increased in the intervention arm.

The VISP trial is an earlier double-blind multicenter RCT that randomized 3,680 patients with a history of recent nondisabling cerebral infarction to a daily multivitamin with either high- or low-dose folate/vitamin B<sub>6</sub>/vitamin B<sub>12</sub> and followed them over a 2-year period. Primary outcome was recurrent ischemic stroke, and secondary outcomes were coronary heart events and death. In this trial, moderate reduction of total homocysteine after nondisabling ischemic stroke had no effect on vascular outcomes during the 2-year follow-up. However, the authors did note a persistent and graded association between baseline total homocysteine level and outcomes. In more specific terms, a 3- $\mu\text{mol/L}$  lower total homocysteine level at baseline was associated with a 10% lower risk of stroke ( $P = .05$ ), a 26% lower risk of cardiovascular events ( $P < .001$ ), and a 16% lower risk of death ( $P = .001$ ). The results were examined in all patients but found to be statistically significant only in the low-dose group. Lower risks were observed in the high-dose group but were nonsignificant.

In 1969, McCully proposed the “homocysteine theory of arteriosclerosis,” which suggested that elevated homocysteine concentrations may be a cause of cardiovascular disease (CVD) in the general population.<sup>3</sup> The first real evidence supporting this theory was published in 1976 when Wilcken

and Wilcken showed that, compared with normal subjects, patients with CAD had higher plasma homocysteine levels following a challenge with oral methionine.<sup>4</sup> Since then, numerous observational studies have led to the conclusion that the association between total homocysteine and CVD is strong, graded, and independent of the conventional vascular risk factors, though the association seems to be largely confined to populations already at high risk of cardiovascular events.<sup>5-8</sup>

Supplementation with B vitamins, particularly folate, reduces total homocysteine concentrations. Thus far, RCTs have failed to show that using folate/B vitamin supplements to reduce homocysteine levels results in fewer cardiovascular events. The “negative” results of the HOPE 2 and VISP trials are echoed in the Bønaa study.<sup>9</sup>

In 2006, Bønaa and colleagues published the results of a double-blind placebo-controlled trial examining the effects of homocysteine-lowering in patients with very recent acute MI. They randomized 3,749 men and women who had an acute MI within 7 days of randomization to one of four regimens: folate/B<sub>12</sub>/B<sub>6</sub> ( $n = 937$ ); folate/B<sub>12</sub> ( $n = 935$ ); B<sub>6</sub> ( $n = 934$ ); and placebo ( $n = 943$ ). Subjects were followed for a median of 40 months with respect to the composite endpoint of recurrent MI, stroke, and sudden death attributable to CAD. There was no benefit with regard to the primary endpoint in any treatment group. In fact, there was a nonsignificant trend toward increased risk in the group given folate/B<sub>12</sub>/B<sub>6</sub> (RR 1.22; 95% CI, 1.00-1.50;  $P = .05$ ). Because of the study design, each group had fewer than 1,000 subjects, and thus the Bønaa study may not have been adequately powered to detect a small effect.<sup>9</sup>

Despite the results of RCTs, consistent findings of an association between total homocysteine level and vascular risk may warrant longer trials in different populations with elevated homocys-

teine levels to find groups who would benefit the most from treatment. Similarly, trials designed to detect smaller reductions in CVD risk with lowering of homocysteine may also be helpful. The HOPE 2 trial was powered to detect a risk reduction of approximately 17% to 20% and may have not been able to detect a smaller risk reduction.<sup>1</sup> Furthermore, current trials cannot distinguish between risk due to elevated homocysteine level and risk due to low folate status, which in itself has been proposed to be a risk factor for CAD independent of homocysteine level.<sup>6</sup>

## CLINICAL BOTTOM LINE

Observational studies suggest a strong correlation between high homocysteine levels and increased risk of cardiovascular events. However, RCTs to date have not shown that lowering plasma homocysteine levels with folate/B vitamins in patients with CVD reduced the risk for the composite endpoint of MI, stroke, and vascular death. JAAPA

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