

Issue 258

In a nutshell

The latest RCT evidence does not support giving Hcy-lowering vitamin supplements to prevent heart disease.

However, a tentative result in preventing stroke, positive outcomes from a few previous but smaller RCTs, and some benefits seen for intermediary outcomes (such as restenosis) in other studies, all suggest that this topic requires more research.

Homocysteine and heart disease in 2006

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NUTRITION RESEARCH REVIEW

Study 1: HOPE 2 trial reports

The HOPE 2 trial of homocysteine (Hcy) lowering in high risk patients recently reported its main findings.

Subjects and method: RCT on 5,522 older adults (mean age 69 yrs) with chronic stable vascular disease. They were given either placebo or vitamins (folic 2.5 mg, B₆ 50 mg, and B₁₂ 1000 µg) over 5 yrs.

Results: Hcy levels fell from a mean of 12.2 to 9.7 µmol/L in the supplemented group, but they enjoyed no advantage over placebo in any outcome measure tested (including cardiovascular incidents and mortality). The exception was risk of stroke, reduced by 25% in the supplemented group. See Graph.

Reference: Lonn E. et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med.* 2006 Apr 13;354(15):1567-77.

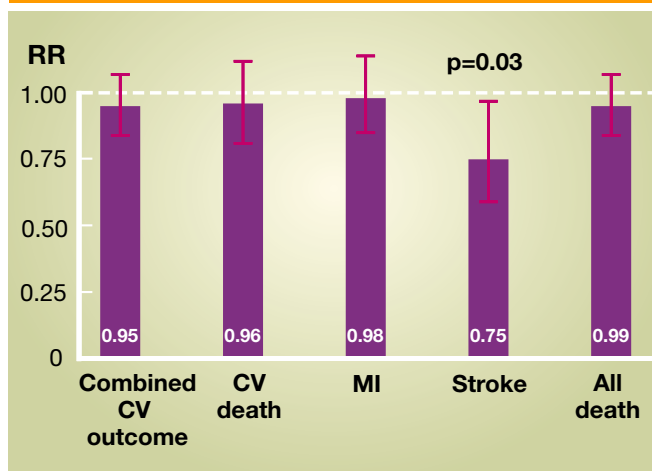
Study 2: NORVIT trial reports

Another trial of homocysteine lowering reported its results in the same journal issue as Study 1.

Subjects and method: RCT on 3,749 patients who had suffered an acute heart attack within the previous 7 days. They were given either placebo, vitamin B₆ alone (40 mg), folate (folic acid 0.8 mg) and B₁₂ (400 µg), or folate, B₁₂ and B₆ together, for 4 yrs.

Results: Folate and B₁₂ together lowered average homocysteine levels by 27%, but there was no significant impact on the combined primary outcome of recurrence of heart attack, stroke or death from CHD. The relative risk of having such an outcome was actually raised in those on the triple vitamin supplement, but this just failed to reach significance (RR=1.22, 95% CI: 1.00-1.50, p=0.05).

Graph: Relative risk: vitamin supplements vs placebo (Study 1)



Reference: Bona KH. et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med.* 2006 Apr 13;354(15):1578-88.

Study 3: Hcy lowering and atherosclerosis

A German trial tested whether reducing Hcy levels affected coronary artery intima-media thickness.

Subjects and method: RCT of 50 patients with intima-medial thickening of the carotid artery, given either placebo or a supplement (folic acid 2.5 mg, B₆ 25 mg, B₁₂ 500 µg) for 1 yr.

Results: Supplements reduced Hcy from 10.5 to 6.56 µmol/L and carotid intima-medial thickness by 5.3% (p=0.034), compared with an increase with placebo.

Reference: Till U. et al. Decrease of carotid intima-media thickness in patients at risk to cerebral ischemia after supplementation with folic acid, Vitamins B6 and B12. *Atherosclerosis.* 2005 Jul;181(1):131-5.

Comments

Elevated total serum homocysteine (Hcy) is a very well established risk factor for cardiovascular disease (CVD), independent of the 'classical' risk factors. It quite strongly predicts both a first and recurring CV incident (including death)¹⁻³. Elevated Hcy adversely affects arterial endothelial function, increases oxidative damage and promotes inflammation and thrombosis⁴. There is a dose-response relationship across a wide range of Hcy levels (including so-called normal range)⁵.

A recent study exemplifies this. Amongst >3,000 patients with chronic heart disease, a subsequent coronary event was 2.5x more likely in patients with elevated compared to normal serum Hcy, and each 5 µmol/L of Hcy predicted a 25% increase in risk⁶.

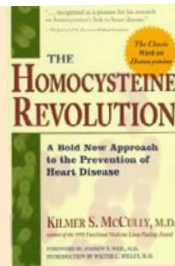
Hcy levels are directly related to status of the nutrients involved in its metabolism, particularly folate and vitamins B₁₂ and B₆, although other nutrients such as riboflavin and carnitine also affect it. It has been estimated that around 2/3 of the prevalence of high homocysteine is due to low vitamin status^{1, 7-9}.

This all makes a very convincing basis for conducting randomised clinical trials using those vitamins to lower Hcy in order to prevent CVD. The first part of the equation - that Hcy levels can be lowered by increasing vitamin intake - has been quite satisfactorily demonstrated in a great many trials (e.g.^{10, 11}), even though some subtleties are not yet fully resolved, such as how much of which vitamins is the ideal way to reduce Hcy levels, the role of genetic variation (MTHFR polymorphism), and the extent to which the Hcy reduction depends on the initial vitamin status^{1, 12-14}.

The middle step in the equation - demonstration that reducing Hcy improves CVD risk factors or intermediary indicators - has also been well studied. The most widely researched intermediary is endothelial function, for which we easily found 21 RCTs involving a wide range of clinical situations and initial Hcy levels (e.g.^{11, 15, 16}). Positive results on endothelial function were reported in 50% of those 21 trials, 41% failed to detect any improvement, and in 9% the outcome was borderline significant or independent of Hcy reduction.

Other trials have found benefits in reduced arterial stiffness, fewer abnormal exercise ECGs, and a non-significant decrease in cerebrovascular atherosclerosis (measured by MRI imaging)¹⁷⁻¹⁹. Of two that looked into the effect of Hcy lowering on inflammatory or haemostatic CVD risk factors, one found a benefit (in renal transplant patients) and the other did not^{20, 21}.

New Study 3 also showed improved intermediary outcome, i.e. carotid arterial intima-media thickening, something previously reported in renal patients²². A related measure, even closer to the ultimate clinical end-points, is the rate of restenosis after angioplasty. A combination Hcy-lowering supplement decreased such relapses in over 500 Swiss patients²³, although in a German trial of over 600 patients (but which used much less B₁₂) it failed to do so²⁴.



Strong epidemiological evidence and a number of clinical trials on intermediary clinical outcomes led many experts to believe that treating elevated Hcy would be important in CVD prevention.

All this paints a picture which, whilst by no means pointing one way, has a definite thread of positive CVD results. So it was disappointing to learn of the clear lack of effect in the two new and large RCTs, Studies 1 and 2. They focused on the ultimate test: incidence of death and other clinical disease outcomes. These add to earlier results from the VISP trial showing that moderate Hcy reductions in 3,680 stroke patients did not benefit any patient outcome measured²⁵.

On the other hand the Swiss trial mentioned above found a reduced rate of 1 yr composite CVD end points²⁶ and a recent, small, open prospective Italian trial in haemodialysis patients reported lowered CVD death and mortality from Hcy reduction²⁷. A reanalysis of the VISP trial data identified a sub-set of 2,155 patients (without renal disease and with initial B₁₂ levels likely to respond to supplements) in whom there was a significant 21% reduction in clinical end points²⁸.

Where does this leave us? It is hard to argue that the new RCTs were lacking in power, or used inadequate vitamin doses. One could wonder whether the average pre-treatment Hcy levels in these trials were high enough, or the amount of Hcy reduction obtained was sufficient, or whether the issue is actually the vitamin levels themselves with Hcy being only an indicator. But, as mentioned above, the earlier evidence suggested the Hcy-CVD link is biological and applies across a broad Hcy range. It is possible that some combination of initial vitamin status and treatment mix could explain the positive RCT results (for example some authors have focused specifically on B₁₂ and its absorption in the elderly¹²), but this currently remains speculation.

On the other hand, whilst what we want to see is benefit in the ultimate clinical end points, it is hard to ignore the reports of Hcy reduction bringing about changes as relevant as less arterial narrowing. Some have theorised that these vitamins have side-effects (e.g. from increased methylation) that counter any benefit from such changes⁵, but at present this too remains in the realm of speculation.

For the moment we cannot say that the data supports the use of Hcy-lowering vitamin supplements. Still, the reduced stroke incidence found in the new HOPE 2 Study and the positive clinical outcomes from the VISP sub-set and Swiss trial all need follow-up. (The new SEARCH trial²⁹ may provide some of those answers).

We continue to recommend the monitoring of B₁₂ and folate status in the elderly and consumption of foods rich in those nutrients. Whether physicians will gain anything from also monitoring Hcy levels is unclear.

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