Commentary

Homocysteine and Cardiovascular Disease: Should We Treat?

Kathleen Potter
School of Medicine and Pharmacology, University of Western Australia, Perth 6000, Australia
For correspondence: Dr Kathleen Potter e-mail: pottek04@cyllene.uwa.edu.au

Homocysteine was first discovered over seventy years ago and has attracted the interest of researchers ever since.[1] The small, sulfur-containing, non-protein-forming amino acid is a key intermediate in the methylation cycle and is produced by all cells during the metabolism of methionine. Excess intracellular homocysteine is exported to the circulation where approximately 1% remains in a free form and the remainder binds to albumin or forms disulfide dimers, principally with cysteine.[2] Total plasma homocysteine (tHcy) is measured as the combined pool of all these forms and has been linked with several diseases. However, it is the relationship between tHcy and cardiovascular disease that has received most attention in the last few decades.

McCully first reported widespread arteriosclerotic lesions in homocysteinuric children at autopsy almost forty years ago.[3] Mudd et al. subsequently confirmed that individuals with cystathionine β-synthase-deficiency, a genetic defect causing severely elevated tHcy, suffered very high rates of premature vascular disease, mainly thromboembolism and stroke.[4] These observations prompted development of a "homocysteine hypothesis": that elevated tHcy contributes to cardiovascular risk in the general population. Epidemiological data establishing an association between elevated tHcy and an increased risk of stroke and myocardial infarction (MI) lent weight to the theory and many plausible mechanisms by which homocysteine might damage the arterial wall or increase the risk of thrombosis have been proposed, although few have been proven unequivocally.[5-10]

A combination of folic acid and vitamin B_{12} reduces tHcy by approximately 25%, even in individuals who are not overtly vitamin-deficient.[11] If elevated tHcy contributes to vascular damage, B-vitamin supplementation might prove a cheap and simple risk-reduction strategy. Consequently, over the last decade several large randomised placebo-controlled trials have tested whether lowering homocysteine reduces cardiovascular risk.[12-18] All trials have reported significant reductions in tHcy in vitamin-treated subjects compared with placebo.[12,14,16,19,20] However, completed trials have largely failed to show that vitamin therapy reduces cardiovascular events or mortality.

Bazzano et al. published the first meta-analysis of trial data in late 2006.[21] The authors analysed data from twelve studies with a combined total of almost 17,000 participants. They found no significant improvement in any of the vascular endpoints or in overall mortality in vitamin-treated subjects compared with placebo. The pooled estimates of relative risk for B-vitamin treated patients were 1.04 (95% CI 0.92, 1.17) for coronary heart disease, 0.86 (95%CI 0.71, 1.04) for stroke and 0.96 (95%CI 0.88, 1.04) for all-cause mortality. While the confidence intervals were consistent with a moderate reduction in the risk of vascular events, there was no unambiguous evidence of benefit.

A more recent meta-analysis included additional data from a large Chinese study and found that folic acid supplementation reduced the risk of stroke by 18% (RR 0·82, 95% CI 0·68, 1·00).[22] Wang et al. also reported that subjects who were treated for more than 36 months or had a greater than 20% reduction in tHcy or had no prior history of stroke experienced more significant risk reduction. This paper, in combination with data showing an improvement in stroke mortality after the introduction of mandatory folic acid fortification in the United States and Canada, has generated speculation that homocysteine-lowering may prove more effective in preventing stroke than other forms of vascular disease.[23-26]

Three additional trials have reported their findings recently, the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS, n=5442), Western Norway B-vitamin Intervention Trial (WENBIT, n=3088) and Homocysteinemia in Kidney and End Stage Renal Disease trial (HOST, n=2056). WAFACS found no difference in the composite endpoint of cardiovascular death, MI, stroke or revascularisation between treatment and placebo groups (RR 1.03, 95% CI 0.9, 1.19) or in any of the individual components of the composite.[27] WENBIT presented initial results on 4 September 2007 at

the European Society of Cardiology Congress in Vienna. The investigators found no difference between folic acid and non-folic acid groups in a composite endpoint of death, non-fatal MI, stroke or hospitalisation with unstable angina (RR 1.09, 95% CI 0.91, 1.30), but have yet to publish detailed data. The HOST trial also reported that B-vitamin treatment in chronic kidney disease did not significantly reduce the risk of all cause mortality, MI or stroke.[19] The editorial accompanying the HOST data updated the Bazzano meta-analysis, reporting an overall odds ratio of 1.00 (95% CI 0.92, 1.09) for coronary heart disease and 0.88 (95% CI 0.78, 1.00) for stroke per 3.1µmol/L reduction in tHcy.[28]

These recent results, added to earlier data, suggest that moderately elevated tHcy is a risk marker for vascular disease rather than a causal risk factor. B-vitamin treatment modifies the marker without reducing the underlying risk. However, the homocysteine hypothesis is not yet disproved. Most large trials have enrolled subjects with existing vascular disease, with end-stage renal failure or with multiple risk factors for atherosclerosis. B-vitamins may prove more effective if treatment is begun prior to the development of clinically evident disease, although this has yet to be demonstrated.

It is also possible that long-term B-vitamin therapy has negative effects that counteract any benefit from reducing tHcy. The Heart Outcomes Prevention Evaluation (HOPE)-2 trial, in 5522 subjects with a history of vascular disease or diabetes, found that the vitamin-treated subjects were more likely to be hospitalised with unstable angina than those on placebo (RR 1.24, 95% CI 1.04, 1.49). This finding might be attributed to chance were it not for previous evidence that B-vitamin therapy increases the risk of in-stent re-stenosis and the need for revascularisation following angioplasty.[12,29] In addition, initial results from the Norwegian Vitamin Trial (NORVIT) presented at the 2005 European Society of Cardiology Congress showed a trend towards an increased cancer rate in folic acid versus non-folic acid groups (RR 1.4, 95% CI 1.0 to 2.0), although this finding was not replicated in data published subsequently.[30] HOPE-2, the only other large trial to publish cancer outcomes, reported a non-significant increase in the relative risk of incident cancer of 1.06 (95% CI 0.91, 1.23).[12] There are plausible biological mechanisms by which folic acid supplementation might increase cancer risk.[31] Actively dividing cells require folate to synthesise DNA and animal studies show that excess folic acid promotes growth of in-situ tumours.[32-34] An abrupt increase in colorectal cancer rates followed the introduction of mandatory food fortification with folic acid in both the USA and Canada, and recent epidemiological data suggests that individuals who take B-vitamin supplements may be at increased risk of breast, prostate and colorectal tumours.[35-39] This new evidence may prompt homocysteine-lowering trialists to re-analyse their data for cancer outcomes.

Several large homocysteine-lowering trials are still ongoing and will provide additional data on the safety and efficacy of long-term B-vitamin supplementation.[15,17,40,41] A meta-analysis including data from more than fifty thousand trial participants is planned and will have adequate power to clearly determine whether lowering tHcy reduces vascular event rates.[42] Currently, however, there is no evidence to support B-vitamin treatment in patients at risk of cardiovascular disease.

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References

1. Butz LW, du Vigneaud V. The formation of a homologue of cysteine by the decomposition of methionine with sulfuric acid. J Biol Chem 1932;99:135-42.
2. Refsum H, Helland S, Ueland PM. Radioenzymic determination of homocysteine in plasma and urine. Clin Chem 1985;31:624-8.
3. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. Am J Pathol 1969;56:111-28.
4. Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilcken B, Pyeritz RE, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genet 1985;37:1-31.
5. Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. Lancet 1999;354:407-13.
6. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA 1995;274:1049-57.
7. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002;325:1202.
8. Casas JP, Bautista LE, Smeeth L, Sharma P, Hingorani AD. Homocysteine and stroke: evidence on a causal link from Mendelian randomisation. Lancet 2005;365:224-32.
9. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 2002;288:2015-22.
10. Weiss N. Mechanisms of increased vascular oxidant stress in hyperhomocysteinemia and its impact on endothelial function. Curr Drug Metab 2005;6: 27-36.
11. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. BMJ

1998;316:894-8.

12. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006;354:1567-77.
13. Bassuk SS, Albert CM, Cook NR, Zaharris E, MacFadyen JG, Danielson E, et al. The Women's Antioxidant Cardiovascular Study: design and baseline characteristics of participants. J Womens Health 2004;13:99-117.
14. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75.
15. VITATOPS Trial Study Group. The VITATOPS (Vitamins to Prevent Stroke) trial: rationale and design of an international, large, simple, randomised trial of homocysteine-lowering multivitamin therapy in patients with recent transient ischaemic attack or stroke. Cerebrovasc Dis 2002;13:120-6.
16. Bonaa KH, Njolstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354:1578-88.
17. Galan P, de Bree A, Mennen L, Potier de Courcy G, Preziozi P, Bertrais S, et al. Background and rationale of the SU.FOL.OM3 study: double-blind randomized placebo-controlled secondary prevention trial to test the impact of supplementation with folate, vitamin B6 and B12 and/or omega-3 fatty acids on the prevention of recurrent ischemic events in subjects with atherosclerosis in the coronary or cerebral arteries. J Nutr Health Aging 2003;7:428-35.
18. Jamison RL, Hartigan P, Gaziano JM, Fortmann SP, Goldfarb DS, Haroldson JA, et al. Design and statistical issues in the homocysteinemia in kidney and end stage renal disease (HOST) study. Clin Trials 2004;1:451-60.
19. Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino PD, et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. JAMA 2007;298:1163-70.
20. Dusitanond P, Eikelboom JW, Hankey GJ, Thom J, Gilmore G, Loh K, et al. Homocysteine-lowering treatment with folic acid, cobalamin, and pyridoxine does not reduce blood markers of inflammation, endothelial dysfunction, or hypercoagulability in patients with previous transient ischemic attack or stroke: A randomized substudy of the VITATOPS trial. Stroke 2005;36:144-6.
21. Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. JAMA 2006;296:2720-6.
22. Wang X, Qin X, Demirtas H, Li J, Mao G, Huo Y, et al. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. Lancet 2007;369: 1876-82.
23. Yang Q, Botto LD, Erickson JD, Berry RJ, Sambell C, Johansen H, et al. Improvement in stroke mortality in Canada and the United States, 1990 to 2002. Circulation 2006;113:1335-43.
24. Hankey GJ. Is homocysteine a causal and treatable risk factor for stroke? The Lancet Neurology 2007;6:751-2.
25. Spence JD. Homocysteine-lowering therapy: a role in stroke prevention? The Lancet Neurology 2007;6: 830-8.
26. Carlsson CM. Lowering homocysteine for stroke prevention. Lancet 2007;369:1841-2.
27. Nainggolan L. Cremation of the homocysteine hypothesis: Another folic-acid trial fails to impress. www.theheart.org/article/753473.do (Accessed 4 December 2007)
28. Baigent C, Clarke R. B vitamins for the prevention of vascular disease: insufficient evidence to justify treatment. JAMA 2007;298:1212-4.
29. Lange H, Suryapranata H, De Luca G, Borner C, Dille J, Kallmayer K, et al. Folate therapy and in-stent restenosis after coronary stenting. N Engl J Med 2004;350:2673-81.
30. Bonaa KH. NORVIT: Randomised trial of homocysteine-lowering with B-vitamins for secondary prevention of cardiovascular disease after acute myocardial infarction. European Society of Cardiology Annual Congress. Stockholm; 2005.http://www.escardio.org/knowledge/OnlineLearning/slides/ESC_Congress_2005/BonaaFP1334/ (Accessed 4 December 2007)
31. Kim YI. Will mandatory folic acid fortification prevent or promote cancer? Am J Clin Nutr 2004;80:1123-8.
32. Choi SW, Mason JB. Folate and carcinogenesis: an integrated scheme. J Nutr 2000;130:129-32.
33. Song J, Medline A, Mason JB, Gallinger S, Kim YI. Effects of dietary folate on intestinal tumorigenesis in the apcMin mouse. Cancer Res 2000;60:5434-40.
34. Bashir O, FitzGerald AJ, Goodlad RA. Both suboptimal and elevated vitamin intake increase intestinal neoplasia and alter crypt fission in the ApcMin/+ mouse. Carcinogenesis 2004;25:1507-15.
35. Mason JB, Dickstein A, Jacques PF, Haggarty P, Selhub J, Dallal G, et al. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological

principles: a hypothesis. Cancer Epidemiol Biomarkers Prev 2007;16:1325-9.

36. Stolzenberg-Solomon RZ, Chang SC, Leitzmann MF, Johnson KA, Johnson C, Buys SS, et al. Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr 2006;83:895-904.
37. Lawson KA, Wright ME, Subar A, Mouw T, Hollenbeck A, Schatzkin A, et al. Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. J Natl Cancer Inst 2007;99:754-64.
38. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007;297:2351-9.
39. Hultdin J, Van Guelpen B, Bergh A, Hallmans G, Stattin P. Plasma folate, vitamin B12, and homocysteine and prostate cancer risk: a prospective study. Int J Cancer 2005;113:819-24.
40. Bostom AG, Carpenter MA, Kusek JW, Hunsicker LG, Pfeffer MA, Levey AS, et al. Rationale and design of the Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) trial. Am Heart J 2006;152:448.e1-7.
41. MacMahon M, Kirkpatrick C, Cummings CE, Clayton A, Robinson PJ, Tomiak RH, et al. A pilot study with simvastatin and folic acid/vitamin B12 in preparation for the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). Nutr Metab Cardiovasc Dis 2000;10:195-203.
42. B-Vitamin Treatment Trialists' Collaboration. Homocysteine-lowering trials for prevention of cardiovascular events: A review of the design and power of the large randomized trials. Am Heart J 2006;151: 282-7.