

Update on homocysteine

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It is now more than 10 years since the first case control and prospective epidemiological studies demonstrated an association between raised plasma homocysteine and increased risk of cardiovascular disease. In that time, most, but not all, epidemiological studies have shown this association to be strong and independent of other cardiovascular risk factors. Generally prospective studies have shown a weaker association than retrospective case control studies (such as the European Concerted Action Project ‘Homocysteinaemia and Vascular Disease’) which have themselves shown a weaker association than retrospective case control studies with non-population-based controls. Thus, studies with a more robust methodology show a weaker association with risk.

So where does this leave us with regard to establishing whether the relationship between homocysteine and cardiovascular disease is likely to be one of cause and effect?

The criteria for causality between a risk factor and a disease are as follows:

1. Is the relationship strong?
2. Is the relationship consistent from study to study?
3. Is there a temporal relationship between risk factor and disease?
4. Is there a dose-response relationship?
5. Is the relationship independent of other risk factors?
6. Does a biologically plausible mechanism exist?
7. Is there evidence that modifying the risk factor modifies the risk?

The relationship between homocysteine and cardiovascular risk is strong and most studies have suggested that a plasma homocysteine level of greater than $12\mu\text{mol/l}$ doubles the risk of cardiovascular disease. The relationship is highly consistent with most prospective and case control studies showing a positive association between the risk factor and the disease.

Most studies suggest a dose-response effect and the relationship has consistently been independent of other traditional cardiac risk factors such as hypercholesterolaemia and hypertension after statistical adjustment for their effect and also independent of non-traditional risk factors such as fibrinogen and lipoprotein (a). The odds ratio for vascular disease per $5\mu\text{mol/l}$ increase in total homocysteine has ranged from as low as 1.1 for prospective studies up to 2.3 for case control studies in meta-analysis of studies of homocysteine and risk.

The temporal relationship between homocysteine and vascular disease was first suggested in patients with homocystinuria, which is inherited as an autosomal recessive disease with 30% of untreated subjects developing a thrombotic event by the age of 30 years and post mortem findings in these patients demonstrating premature vascular disease pathology. Genetic and cohort studies indicate also that the increase in plasma homocysteine precedes the occurrence of vascular disease rather than being caused by it.

Many mechanisms whereby homocysteine may be atherothrombotic have been described. In particular, homocysteine has adversely affected endothelial function with endothelial dysfunction demonstrated using flow-mediated dilatation even in patients with moderate elevation of plasma homocysteine. It is proposed that this may be via impaired nitric oxide (NO) release at the level of the vascular endothelium.

Platelet function may be affected with increased biosynthesis of thromboxane A₂ (a potent vasoconstrictor) leading to platelet activation *in vivo*. Lipid metabolism may also be altered and LDL oxidation by homocysteine has been shown *in vitro* but not yet in living models. Coagulation cascade studies have shown enhanced tissue factor activation, reduced von Willebrand factor, increased fibrinogen levels and reduced binding of tissue plasminogen factor to endothelial cells. Effects of homocysteine on smooth muscle growth and proliferation have also been demonstrated as well as direct cellular toxicity.

The final criterion needed for causality is proof that reducing homocysteine levels will actually reduce the incidence of vascular events. It is clear that vitamin supplementation with folic acid, vitamin B₆ and vitamin B₁₂ will reduce homocysteine levels, but it is not known if a reduction in cardiovascular risk results. Currently there are at least seven randomised, controlled trials underway (see Table 1) each of which involves several thousand patients and supplementing doses of folate varying from $200\mu\text{g}$ to 5mg and several doses of B₆ and B₁₂ in an attempt to answer this last part of the puzzle.

Until the results of these trials are reported in 3-4 years time we cannot make any decisions on causality. However on the assumption that lowering plasma homocysteine will reduce the progression of atherosclerosis, it has been estimated that increasing dietary folate alone via fruit and vegetables would have a substantial effect on cardiovascular

morbidity. This is because a 40% increase in dietary folate would prevent 2% of cardiovascular deaths, while folic acid supplements would reduce 4% of deaths. What seems likely from our own European study is that homocysteine probably increases the risk associated with conventional risk factors such as smoking. Thus, risk factor control should be meticulous in subjects with heart disease and a raised plasma homocysteine.

In the meantime, we would suggest that in the majority of subjects with even moderately elevated homocysteine there is *probably* a benefit from reducing homocysteine

level with increased dietary folate, B12 and B6, either in the form of increased consumption of fruit fibre and green vegetables, or as an oral folic acid supplement for high risk subjects with above normal homocysteine. Until we know more, the adage “eat right and take a multivitamin” would appear to hold true.

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Table 1
Vitamin trials to evaluate the relationship between elevated plasma homocysteine and cardiovascular disease risk.

Trial title	Patient population	Sample size	Vitamin therapy
VISP Vitamin Intervention in Stroke Prevention	Stroke	3600	Folic acid 2.5mg+25mg +B12400µg versus folic acid 200µg+B6 200µg +B12 60µg
WACS Women's Antioxidant and Cardiovascular Disease Study	Vascular disease or high risk	6-8000	Folic acid 2.5mg+B6 50mg +B12 1mg versus placebo
SEARCH Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine	Myocardial infarction	12000	Folic acid 2mg+B12 1mg versus placebo in a 2x2 factorial design with simvastatin 80mg versus 20mg
NORVIT Norwegian Study of Homocysteine Lowering with B-Vitamins in Myocardial Infarction	Myocardial infarction	3000	Folic acid 5mg x 2 weeks+800µg +B12 400µg versus placebo in a 2x2 factorial design with B6 40mg versus placebo
BERGEN VITAMIN STUDY	Coronary heart disease	2000	Folic acid 5mg x 2 weeks +800µg +B12 400µg versus placebo in a 2x2 factorial design with B6 40mg versus placebo
PACIFIC Prevention with a combined ACE inhibitor and folate in coronary heart disease	High risk or previous vascular disease	10000	Folic acid 200µg or 2mg versus placebo in 2x2 factorial design with omapatrilat
CHAOS-2 Cambridge Heart Antioxidant Study	Myocardial infarction or unstable angina	4000	Folic acid 5mg versus placebo