

First update, July 2007

Chapter 20: Cardiovascular diseases: Mann & Chisholm

PLASMA HOMOCYSTEINE – MOVE TO RANDOMISED CONTROLLED TRIALS – Update of 20.4.8

In 20.4.8 (page 294) “Homocysteine is an independent risk factor for CHD Folic acid and vitamins B-6 and B-12 can reduce raised homocysteine levels. There is as yet no definitive evidence that reducing homocysteine levels can reduce clinical CHD”. A paragraph in 12.7.7 (chapter 7) indicates that the evidence is in the form of accumulating observational studies.

Here was a situation in which the association could be further tested by randomised controlled trials (RCTs). A daily dose of 500µg or more of folic acid lowers homocysteine. This is somewhat more than the RDI but within the range of normal intakes. The most economical trials will be in people at increased risk of a cardiovascular disease event, ie, secondary prevention trials.

In the NORVIT Trial (1) subjects had had a previous acute myocardial infarction. They were randomly allocated to 800 µg per day folic acid or placebo and 3750 men and women were followed up for 40 months. In the HOPE 2 trial (2) patients had a history of CHD or other vascular disease or diabetes. Folic acid 2,500 µg/day or placebo was taken for 5 years. Extra vitamins B-6 and B-12 were given with the folic acid in both trials. Results were disappointing in these, and other trials reporting in 2006 and 2007. In HOPE 2 there were however fewer ischaemic strokes (P0.03) in those on folic acid. Numbers were small in this subgroup and the authors cautiously made no claim.

As explained in 12.7.8 people with the less common TT variant at 667 in the 5,10-methylene THF reductase enzyme (MTHFR) have lower blood folate and higher homocysteine than those with the CC genotype. Casas et al (3) collected published data on MTHFR genotype and stroke (30 reports) for a meta-analysis. They found the odds ratio for strokes was 1.26 for TT versus CC, a modest but significant effect. The difference determining plasma homocysteine here is Mendelian, not environmental.

Since then Wang et al have carried out a meta-analysis of the 8 eligible RCTs with folic acid and stroke as outcome (4). There were over 16,000 participants and 778 stroke events. Pooling all 8 trials, folic acid supplements (with or without other B vitamins) significantly reduced the risk of stroke by 18%. The effect was less in countries with mandatory folate fortification, with shorter duration trials and in the one trial in people with a history of previous strokes. Thus it would seem that extra folate can contribute to reducing strokes, but not CHD.

This is plausible. Risk factors for stroke differ in strength from those for CHD. Raised plasma cholesterol has a weaker effect; hypertension has a stronger effect on risk of stroke – and so does raised homocysteine in observational epidemiology. The big picture is consistent. Since grains have been fortified in North America plasma homocysteines are lower (chapter 12.7.7) and stroke mortality has declined faster there than in England and Wales (where fortification is not mandatory).

If increased folate and lower homocysteine help reduce strokes, could they contribute to delaying dementia of old age? Cerebral vascular disease is the second major cause of dementia and people with dementia have lower serum folate and vitamin B-12 and higher homocysteine (the lower vitamin levels could be result of poor diets). Several RCTs of folate supplementation and cognitive function have been reported recently. Only two of these have run for at least 2 years, gave at least 1,000 µg/day folic acid and used multiple tests of cognitive function. In both these trials subjects were apparently healthy and those with low plasma homocysteine were screened out. The RCT by Professor Jim Mann's group (5) in Otago found no benefit in the group that received folic acid plus vitamins B6 and B-12. But a trial in the Netherlands (6) found improvement after 3 years with folic acid in information processing speed and memory, not in other functions. The Standard Mini-Mental State Examination was not affected. It is possible that the partly positive results in the Dutch RCT were because they had more subjects, followed for longer and their subjects were younger. The question remains whether age-related cognitive decline is, or is not an early stage of dementia.

Fortification of cereal grains with folate across North America from 1998 is being watched by nutrition scientists for any effects. Concern remains that high folate levels could

aggravate symptoms in people deficient in vitamin B-12. Morris et al, at Tufts University (7) have recently found, in the 1999-2002 US National Health & Nutrition Examination Survey, that seniors with low vitamin B-12 status had more cognitive impairment and anaemia if their serum folate was higher.

References

1. Bøuaa KH, Njølstad I, Ueland PM, et al. (2006) Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Eng J Med*, 354 : 1578-88.
2. Lonn E, Yusuf S, Arnold MJ, et al. (2006) Homocysteine lowering with folic acid and B vitamins in vascular disease. The Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. *N Eng J Med*, 354 : 1567-77.
3. Casas JP, Bautista LE, Smeeth L, Sharma P & Hingorani AD (2005) Homocysteine and stroke : evidence on a causal link for mendelian randomisation. *Lancet*, 365 : 224-32.
4. Wang X, Qin X, Demartas H, et al. (2007) Efficacy of folic acid supplementation in stroke prevention : a meta-analysis. *Lancet*, 369 : 1876-82.
5. McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI & Williams SM (2006) A controlled trial of homocysteine lowering and cognitive performance. *N Eng J Med*, 354 : 2764-72.
6. Durga J, van Boxtel MPJ, Schouten EC, Kok FJ, Jolles J, Katan MB & Verhoef P (2007) Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial : a randomised double blind controlled trial. *Lancet*, 369 : 208-16.
7. Morris MS, Jacques PF, Rosenberg IH & Selhub J (2007) Folate and vitamin B-12 status in relation to anaemia, macrocytosis and cognitive impairment in older Americans in the age of folic acid fortification. *Am J Clin Nutr*, 85 : 193-209.