Major journals

No cardiovascular benefits seen with high-dose vitamin B

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Numerous epidemiological studies have demonstrated an association between elevated plasma homocysteine levels and the risk of cardiovascular disease. This study (summarised on right) evaluated the efficacy of homocysteine-lowering treatment with B vitamins for secondary prevention in people who had suffered an acute myocardial infarction (MI).

In total, 3749 men and women with an MI within 7 days prior to randomisation received, in a two-by-two factorial design: 0.8 mg of folic acid, 0.4 mg of vitamin B_{12} and 40 mg of vitamin B_6; 0.8 mg of folic acid and 0.4 mg of vitamin B_{12}; 40 mg of vitamin B_6; or placebo. The primary endpoint during a median follow-up of 40 months was a composite of recurrent MI, stroke and sudden cardiac death.

The mean total homocysteine level in those receiving folic acid plus vitamin B_{12} was lowered by 27 %, with no significant effect on the primary endpoint; similarly, in the group receiving vitamin B_6 there was no significant benefit in terms of the primary endpoint. In the group given folic acid, vitamin B_6 and vitamin B_{12}, there was a trend toward increased risk (relative risk, 1.22, 95 % confidence interval, 1.00–1.50; $P=0.05$).

Despite a substantial reduction in plasma homocysteine levels, these results are contrary to expectation. Non-compliance does not appear to be a likely explanation; similarly, the statistical power of the study is also an unlikely explanation. As the inclusion criteria for this study were wide and a large variety of people were included, it is likely that the results of this study may be applicable to most people with acute MI.

An epidemiological association between homocysteine and cardiovascular disease but no causative role for homocysteine has been identified from intervention trials using homocysteine-reducing therapy. The failure of this study to show any cardiovascular benefits with high-dose vitamin B supplementation is similar to the results seen with high-dose vitamin C and E, and should encourage more research to be conducted using more physiological dosages of such vitamins.

Folic acid in combination with vitamin B_6 may reduce the rate of restenosis following angioplasty, but may increase the rate following coronary stenting; the latter findings being seen with similar dosages as used in this study. Folic acid and homocysteine-lowering therapy has been shown to improve vascular function. However, the results of this study suggest that such treatments may have an effect to promote atherothrombosis, with potential mechanisms including an increased proliferation of vascular smooth muscle cells, effects on vascular remodelling and myocardial repair.

In summary the results of this study illustrate that folic acid with or without vitamin B supplementation had no effect on cardiovascular outcomes and may even prove harmful. This further demonstrates that interventions that may improve surrogate markers of cardiovascular disease may not translate into reductions in cardiovascular mortality.

NEW ENGLAND JOURNAL OF MEDICINE

B vitamins did not lower CV risk

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Studies have shown that the plasma total homocysteine level is a strong, graded and independent risk factor for coronary heart disease (CHD) and stroke.

2 The authors evaluated the efficacy of homocysteine-lowering treatment with B vitamins for secondary prevention in 3749 people who had suffered a myocardial infarction (MI) within 7 days before randomisation.

3 Patients were randomly allocated into daily treatments of one of the following groups: 0.8 mg folic acid, 0.4 mg vitamin B_{12} and 40 mg vitamin B_6; 0.8 mg folic acid and 0.4 mg vitamin B_{12}; 40 mg vitamin B_6; or placebo.

4 The primary endpoint during a mean follow-up of 36 months was a composite recurrent MI, stroke and sudden death attributed to CHD.

5 The mean total homocysteine level was lowered by 27 % among the group taking folic acid plus vitamin B_{12}, but this treatment had no significant effect on the primary endpoint.

6 Treatment with vitamin B_6 alone was also not associated with any significant benefit with regard to the primary endpoint.

7 In the group taking folic acid, vitamin B_{12} and vitamin B_6, there was a trend toward an increased risk of cardiovascular (CV) events.

8 Treatment with B vitamins did not lower the risk of recurrent CV disease after acute MI. Such therapy may be harmful after acute MI, and should be avoided.

Bonaa KH, Njolstad I, Ueland PM et al (2006) Homocysteine-lowering and cardiovascular events after acute myocardial infarction. *New England Journal of Medicine* **354**: 1578–88

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Statin therapy reduces LDL-C

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Intravascular ultrasound (IVUS) imaging is the predominant approach for evaluating the progression of coronary atherosclerosis.

2 Positive IVUS trials have shown a slowing or halting of the progression of atherosclerosis during statin treatment.

3 The hypothesis tested was that high-intensity statin therapy, designed to reach low levels of low-density lipoprotein cholesterol (LDL-C), with substantial elevation of high-density lipoprotein cholesterol (HDL-C), might result in regression of coronary atherosclerosis.

4 Baseline IVUS examinations were measured in 507 patients who recieved at least one dose of the study drug (rosuvastatin); after 24 months of treatment, 349 people had evaluable IVUS examinations.

5 The mean baseline LDL-C level of 130.4 mg/dl (3.34 mmol/l) declined to 60.8 mg/dl (1.56 mmol/l; a 53.2% reduction) after very high-intensity statin therapy of rosuvastatin 40 mg daily. Approximately 75% of participants achieved a mean LDL-C level <70 mg/dl (<1.79 mmol/l) during treatment.

6 The mean HDL-C level at baseline was 43.1 mg/dl (1.11 mmol/l), which increased to 49.0 mg/dl (1.26 mmol/l; a 14.7% increase) during very high-intensity statin therapy.

7 Treatment to LDL-C levels below currently accepted guidelines, with significant HDL-C increases, can regress atherosclerosis in people with coronary disease.

Nissen SE, Nicholls SJ, Sipahi I et al (2006) Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. *Journal of the American Medical Association* **295**: 1556–65

BRITISH MEDICAL JOURNAL

Smoking affects glucose levels

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The hypothesis tested was that current smokers (n=1386 and 621 previous smokers) would have a higher incidence of impaired fasting glucose and diabetes during follow-up (15 years) than never smokers exposed to secondhand smoke (n=1452) and never smokers with no smoke exposure (n=1113).

2 During follow-up, 16.7% developed glucose intolerance.

3 The 15-year incidence of glucose intolerance was 21.8% for smokers, 17.2% for never smokers with passive smoke exposure, 14.4% for previous smokers and 11.5% for never smokers with no smoke exposure.

Houston TK, Person SD, Pletcher MJ et al (2006) Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort. *British Medical Journal* **332**: 1064–9

ARCHIVES OF INTERNAL MEDICINE

Ramipril lowers diabetes risk

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The African American Study of Kidney Disease and Hypertension was a trial of 1094 people with hypertensive kidney disease randomised to an angiotensin-converting enzyme inhibitor, a ß-blocker or a calcium channel blocker.

2 Follow-up was 3.0–6.4 years. The analysis was designed to examine two main outcome variables: diabetes and a composite of impaired fasting glucose or diabetes.

3 Among 1017 participants, 147 (14.5%) developed diabetes; 333 out of 776 (42.9%) developed impaired fasting glucose or diabetes.

4 Respective event rates for diabetes were 2.8%, 4.4% and 4.5% per patient per year in the angiotensin-converting enzyme inhibitor-, calcium channel blocker- and ß-blocker-treated groups.

5 Treatment with an angiotensin-converting enzyme inhibitor (ramipril) was associated with a significantly lower risk of diabetes.

Thornley-Brown D, Wang X, Wright JT et al (2006) Differing effects of antihypertensive drugs on the incidence of diabetes mellitus among patients with hypertensive kidney disease. *Archives of Internal Medicine* **166**: 797–805

BRITISH MEDICAL JOURNAL

Statins reduce coronary events

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 This study evaluated and compared the efficacy of lipid-lowering drug treatment (e.g. statins) in people with and without diabetes from 12 randomised, placebo-controlled, double-blind trials with a follow up of at least 3 years.

2 Lipid-lowering drug treatment was found to be as least as effective in people with diabetes as in those without diabetes.

3 In primary prevention, the risk reduction for major coronary events was 21% in people with diabetes versus 23% in those without; however, the absolute risk difference was three times higher in secondary prevention.

4 People with diabetes benefit more from lipid-lowering drugs.

Costa J, Borges M, David C, Vaz Carneiro A (2006) Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients. *British Medical Journal* **332**: 115–24

'Treatment with an angiotensin-converting enzyme inhibitor (ramipril) was associated with a significantly lower risk of diabetes.'