Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

THERAPEUTICS

Lowering homocysteine with folic acid and B vitamins did not prevent vascular events in vascular disease

Lonn E, Yusuf S, Arnold MJ, et al. **Homocysteine lowering with folic acid and B vitamins in vascular disease.** N Engl J Med. 2006;354:1567-77.

Clinical impact ratings: GIM/FP/GP ★★★★★★★ Cardiology ★★★★★★☆ Endocrinology ★★★★★★☆ Neurology ★★★★★★☆

QUESTION

In patients with vascular disease, does lowering plasma homocysteine levels with folic acid and B vitamins reduce risk for major vascular events?

METHODS

Design: Randomized placebo-controlled trial (Heart Outcomes Prevention Evaluation [HOPE] 2 trial).

Allocation: Concealed.*

Blinding: Blinded {clinicians, patients, data collectors, outcome assessors, and data analysts}†.*

Follow-up period: Mean 5 years.

Setting: 145 centers in 13 countries (Canada, United States, Brazil, western Europe, and Slovakia).

Patients: 5522 patients ≥ 55 years of age (mean age 69 y, 72% men) with a history of coronary artery, cerebrovascular, or peripheral artery disease, or diabetes with ≥ 1 risk factor for atherosclerosis. 54% of patients had a history of myocardial infarction (MI), and 9% had a history of stroke. Patients were eligible regardless of homocysteine levels. Exclusion criteria included planned revascularization and other types of significant cardiovascular disease (CVD).

Intervention: A combined pill with 2.5 mg folic acid, 50 mg vitamin B_6, and 1 mg vitamin B_{12} taken once daily (n = 2758), or placebo (n = 2764).

Outcomes: A composite endpoint of MI, stroke, or death from CV causes. Secondary outcomes included total ischemic events (primary outcome components plus hospitalization for unstable angina or revascularization), death from any cause, hospitalization for unstable angina, and revascularization.

Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

Mean baseline homocysteine level was 12.2 µmol/L (1.6 mg/L). In a randomly selected subgroup of 21% of patients, the mean homocysteine level at 2 years decreased by 2.2 µmol/L (0.3 mg/L) in the intervention group and increased by 1.1 µmol/L (0.1 mg/L) in the placebo group. Groups did not differ for the primary composite endpoint, total ischemic events, or death from any cause (Table). Hospitalization for unstable angina was increased in the intervention group (Table).

CONCLUSION

In patients with vascular disease, lowering plasma homocysteine levels with folic acid and B vitamins did not reduce risk for the composite endpoint of myocardial infarction, stroke, or death from cardiovascular causes more than placebo.

Sources of funding: Canadian Institutes of Health Research. Study drugs provided by Jamieson Laboratories.

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*See Glossary.

†Information provided by author.

Folic acid and vitamins B_6 and B_{12} (intervention) vs placebo to prevent vascular events in vascular disease‡

Outcome	Intervention	Placebo	RRR (95% CI)	NNT
Composite endpoint§	19%	20%	5% (–7 to 16)	Not significant
Death from any cause	17%	17%	1% (–13 to 12)	Not significant
			RRI (CI)	NNH (CI)
Total ischemic events	33%	32%	3% (–6 to 13)	Not significant
Unstable angina	9.7%	7.9%	24% (4 to 49)	53 (26 to 317)
Revascularization	17%	15%	10% (–4 to 26)	Not significant

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from control event rates and relative risks in article.
§Myocardial infarction, stroke, or death from cardiovascular causes.

COMMENTARY

It's déjà vu all over again. On the basis of a plausible biological rationale, observational studies consistently showing an association between a risk factor and subsequent CVD, and small experimental studies showing an effect of the intervention on surrogate endpoints, it is proposed that a cheap and simple pill can have a dramatic effect on CV outcomes. In this case, the cheap and simple pill is a combination of folic acid and B vitamins. The hypothesis is that taking this pill will reduce plasma levels of homocysteine (which a large body of epidemiologic evidence shows is associated with CV risk) and that this effect will, in turn, reduce CV events.

This compelling rationale has now been tested in 3 related randomized controlled trials. The first trial compared a high-dose combination of folate and B vitamins with a control pill of low doses of the same vitamins in 3680 patients who had recently had a nondisabling stroke and had fasting total homocysteine levels > 25th percentile for stroke patients (1). Despite documented increases in blood levels of folate and vitamin B_{12}, the intervention had no effect on stroke, a composite endpoint of coronary events, or death over a 2-year period.

These disappointing results were reinforced by the findings of the HOPE-2 and NORVIT trials. In HOPE-2, men and women ≥ 55 years of age with CVD, 55% and 40% of whom had hypertension and diabetes, respectively, were randomized to a combination of folate and vitamins B_6 and B_{12} or placebo. Despite an average 22% reduction in plasma homocysteine levels, there was no effect of the intervention on the composite endpoint of CVD death, MI, or stroke. In analyses of each outcome separately, a beneficial effect of the intervention on stroke was observed, but this is unlikely to be a causal association, since such an effect was not observed in either of the other 2 trials. Like the authors of HOPE-2, I believe this finding was an overestimate of the effect or due to chance.

In NORVIT, 3749 patients with recent MI were randomized to placebo, folate and vitamin B_{12}, vitamin B_6, or the combination of folate and vitamins B_{12} and B_6. These treatments predictably lowered plasma homocysteine levels by an average of 27%. However, after more

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Lowering homocysteine with folic acid and B vitamins did not prevent vascular events after myocardial infarction

Bønaa KH, Njølstad I, Ueland PM, et al. **Homocysteine lowering and cardiovascular events after acute myocardial infarction.** N Engl J Med. 2006;354:1578-88.

Clinical impact ratings: GIM/FP/GP ★★★★★★★ Cardiology ★★★★★★☆

QUESTION

In patients with acute myocardial infarction (MI), does lowering plasma homocysteine levels with folic acid plus vitamin B_{12} or vitamin B_6 reduce risk for major vascular events?

METHODS

Design: Randomized, 2 × 2 factorial design, placebo-controlled trial (Norwegian Vitamin [NORVIT] trial).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, data collectors, and outcome assessors).*

Follow-up period: 2.0 to 3.5 years (median 3.3 y).

Setting: 35 hospitals in Norway.

Patients: 3749 patients 30 to 85 years of age (mean age 63 y, 74% men) with acute MI in the previous 7 days. Exclusion criteria included life expectancy < 4 years.

Intervention: A combined capsule with 0.8 mg folic acid, 40 mg vitamin B_6, and 0.4 mg vitamin B_{12} (n = 937); 0.8 mg folic acid and 0.4 mg vitamin B_{12} (n = 935); 40 mg vitamin B_6 (n = 934); or placebo (n = 943), taken once daily. The 2 folic acid groups received a loading dose of 5 mg folic acid daily for 2 weeks.

Outcomes: A composite endpoint of MI, stroke, or sudden death from coronary heart disease. Secondary outcomes included MI, stroke, hospitalization for unstable angina, coronary revascularization, and death from any cause.

Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

Mean baseline homocysteine levels were 12.9 to 13.3 µmol/L (1.7 to 1.8 mg/L). Mean homocysteine level at 2 years decreased by 3.4 to 3.7 µmol/L (0.5 mg/L) in the 2 folic acid groups and increased by 0.4 to 0.5 µmol/L (0.1 mg/L) in the 2 groups without folic acid. Groups did not differ for any clinical outcome (Table).

CONCLUSIONS

In patients with myocardial infarction, lowering plasma homocysteine levels with folic acid and vitamin B_{12}, with or without vitamin B_6, did not reduce risk for the composite endpoint of myocardial infarction, stroke, or death from coronary heart disease. The use of vitamin B_6, with or without folic acid and vitamin B_{12}, also did not reduce risk.

Sources of funding: Norwegian Research Council; Council on Health and Rehabilitation; Norwegian Council on Cardiovascular Disease; Northern Norway Regional Health Authority; Norwegian Red Cross; Foundation to Promote Research into Functional Vitamin B_{12} Deficiency; private donation. Study drugs provided by Alpharma.

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*See Glossary.

Folic acid plus vitamin B_{12} and vitamin B_6, separately and in combination, to prevent vascular events after myocardial infarction†

Outcomes	RRR/RRI (95% CI)		
	Folic acid/B_{12} vs no folic acid/B_{12}	B_6 vs no B_6	Folic acid/B_{12}/B_6 vs placebo
Composite endpoint‡	RRI: 8% (–7 to 25)	RRI: 14% (–2 to 32)	RRI: 22% (0 to 50)
Myocardial infarction	RRI: 6% (–9 to 24)	RRI: 17% (0 to 37)	RRI: 23% (–1 to 52)
Stroke	RRI: 2% (–32 to 51)	RRR: 19% (–20 to 46)	RRR: 17% (–47 to 53)
Death from any cause	RRI: 2% (–17 to 26)	RRI: 19% (–4 to 46)	RRI: 21% (–9 to 61)
Unstable angina	RRI: 6% (–11 to 27)	RRR: 12% (–5 to 26)	RRR: 7% (–19 to 27)
Coronary artery bypass surgery	RRR: 10% (–5 to 24)	RRR: 1% (–17 to 16)	RRR: 11% (–13 to 29)
Percutaneous coronary intervention	RRR: 8% (–3 to 18)	RRR: 6% (–5 to 17)	RRR: 14% (–2 to 28)

†Abbreviations defined in Glossary; RRR, RRI, and CI calculated from data in article. All comparisons were not significant.
‡Myocardial infarction, stroke, or death from coronary heart disease.

COMMENTARY *(continued from page 2)*

than 3 years, not only was there no evidence of a benefit, the combination-vitamin group had a trend toward an increase in the composite endpoint of fatal or nonfatal MI, stroke, or sudden cardiac death.

Proponents point to the lower (but not statistically significant) relative risk seen in HOPE-2 in the countries in which folate fortification of food is not routine and the slight divergence of the Kaplan-Meier curves beyond year 4 as evidence that the folate-homocysteine hypothesis might yet be correct. They claim that what is needed to see an effect is simply more time and folate supplementation in appropriately "folate-deficient" populations. Perhaps, but I doubt it. The plasma total homocysteine level in the whole HOPE-2 sample was at a value (about 12 µmol/L) that has been associated, in observational studies, with increased risk for CVD events. In HOPE-2, lowering this level of homocysteine by about 20% produced no change in CVD outcomes.

These results are distressingly familiar to anyone who has followed the stories about vitamin E and postmenopausal hormone therapy for prevention of CVD. The conclusion, in my opinion, is that in CVD prevention there is simply no substitute for large randomized controlled trials that measure clinical—and not surrogate—endpoints. To do otherwise risks chasing rainbows, while putting insufficient effort into ensuring that all eligible patients are receiving therapy proven to save lives.

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Reference

1. **Toole JF, Malinow MR, Chambless LE, 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.