

# Abstract

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## Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial.

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage JM, Bowman L, Clarke RJ, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Sleight P, Peto R, Collins R.

**CONTEXT:** Blood homocysteine levels are positively associated with cardiovascular disease, but it is uncertain whether the association is causal.

**OBJECTIVE:** To assess the effects of reducing homocysteine levels with folic acid and vitamin B(12) on vascular and nonvascular outcomes.

**DESIGN, SETTING, AND PATIENTS:** Double-blind randomized controlled trial of 12,064 survivors of myocardial infarction in secondary care hospitals in the United Kingdom between 1998 and 2008.

**INTERVENTIONS:** 2 mg folic acid plus 1 mg vitamin B(12) daily vs matching placebo.

**MAIN OUTCOME MEASURES:** First major vascular event, defined as major coronary event (coronary death, myocardial infarction, or coronary revascularization), fatal or nonfatal stroke, or noncoronary revascularization.

**RESULTS:** Allocation to the study vitamins reduced homocysteine by a mean of 3.8 micromol/L (28%). During 6.7 years of follow-up, major vascular events occurred in 1537 of 6033 participants (25.5%) allocated folic acid plus vitamin B(12) vs 1493 of 6031 participants (24.8%) allocated placebo (risk ratio [RR], 1.04; 95% confidence interval [CI], 0.97-1.12; P = .28). There were no apparent effects on major coronary events (vitamins, 1229 [20.4%], vs placebo, 1185 [19.6%]; RR, 1.05; 95% CI, 0.97-1.13), stroke (vitamins, 269 [4.5%], vs placebo, 265 [4.4%]; RR, 1.02; 95% CI, 0.86-1.21), or noncoronary revascularizations (vitamins, 178 [3.0%], vs placebo, 152 [2.5%]; RR, 1.18; 95% CI, 0.95-1.46). Nor were there significant differences in the numbers of deaths attributed to vascular causes (vitamins, 578 [9.6%], vs placebo, 559 [9.3%]) or nonvascular causes (vitamins, 405 [6.7%], vs placebo, 392 [6.5%]) or in the incidence of any cancer (vitamins, 678 [11.2%], vs placebo, 639 [10.6%]).

**CONCLUSION:** Substantial long-term reductions in blood homocysteine levels with folic acid and vitamin B(12) supplementation did not have beneficial effects on vascular outcomes but were also not associated with adverse effects on cancer incidence.

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