ORIGINAL ARTICLE

Homocysteine Lowering and Cardiovascular Events after Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

Homocysteine is a risk factor for cardiovascular disease. We evaluated the efficacy of homocysteine-lowering treatment with B vitamins for secondary prevention in patients who had had an acute myocardial infarction.

METHODS

The trial included 3749 men and women who had had an acute myocardial infarction within seven days before randomization. Patients were randomly assigned, in a two-by-two factorial design, to receive one of the following four daily treatments: 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 end point during a median follow-up of 40 months was a composite of recurrent myocardial infarction, stroke, and sudden death attributed to coronary artery disease.

RESULTS

The mean total homocysteine level was lowered by 27 percent among patients given folic acid plus vitamin B_{12}, but such treatment had no significant effect on the primary end point (risk ratio, 1.08; 95 percent confidence interval, 0.93 to 1.25; P=0.31). Also, treatment with vitamin B_6 was not associated with any significant benefit with regard to the primary end point (relative risk of the primary end point, 1.14; 95 percent confidence interval, 0.98 to 1.32; P=0.09). In the group given folic acid, vitamin B_{12}, and vitamin B_6, there was a trend toward an increased risk (relative risk, 1.22; 95 percent confidence interval, 1.00 to 1.50; P=0.05).

CONCLUSIONS

Treatment with B vitamins did not lower the risk of recurrent cardiovascular disease after acute myocardial infarction. A harmful effect from combined B vitamin treatment was suggested. Such treatment should therefore not be recommended. (ClinicalTrials.gov number, NCT00266487.)

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Case–control as well as prospective studies have demonstrated that the plasma total homocysteine level is a strong, graded, and independent risk factor for coronary heart disease (CHD) and stroke.[1-3] Evidence from studies involving so-called mendelian randomization,[4] demonstrating an association between CHD and the 677C→T methylenetetrahydrofolate reductase polymorphism, has provided additional support for a causal relation between homocysteine and CHD.[5,6]

Plasma total homocysteine can be lowered with the B vitamins folic acid and vitamin B_{12},[7] and persons with high plasma levels or dietary intake of folate and vitamin B_6 have a decreased risk of CHD.[8-11] The lowering of the population mean level of total homocysteine in the United States by fortifying food with folic acid[12] is estimated to have prevented 17,000 deaths from coronary causes each year,[13] and the inclusion of folic acid in a combination pill has been suggested as a means to prevent cardiovascular disease.[14]

In contrast to what was expected on the basis of epidemiologic evidence, the first large, randomized trial found that lowering the total homocysteine level with B vitamins failed to prevent recurrent stroke, myocardial infarction, or death in patients who had had a recent stroke.[15] A post hoc efficacy analysis indicated, however, that a large subgroup of the participants in the trial might have benefited from B vitamin treatment.[16] Studies of the effects of B vitamins on the risk of restenosis after percutaneous coronary intervention have also yielded inconsistent results.[17,18] We conducted a large trial to evaluate the potential benefit of such therapy in patients after acute myocardial infarction.

METHODS

STUDY POPULATION AND DESIGN

The Norwegian Vitamin (NORVIT) trial was a multicenter, prospective, randomized, double-blind, placebo-controlled evaluation of the potential benefit of B vitamin therapy in patients with an acute myocardial infarction. Study medication was provided without charge by Alpharma. The sponsors had no role in the design, conduct, or reporting of the study. The protocol was approved by the regional committee for research ethics. All participants provided written informed consent.

Men and women 30 to 85 years of age who had had an acute myocardial infarction within seven days before randomization were eligible to participate. Exclusion criteria were the presence of coexisting disease associated with a life expectancy of less than four years, prescribed treatment with B vitamins or untreated vitamin B deficiency, or inability to follow the protocol, as judged by the investigator.

Participants were randomly assigned, in a two-by-two factorial design, to receive one of the following four treatments: 0.8 mg of folic acid, 0.4 mg of vitamin B_{12}, and 40 mg of vitamin B_6 per day (referred to as combination therapy); 0.8 mg of folic acid plus 0.4 mg of vitamin B_{12} per day; 40 mg of vitamin B_6 per day; or placebo. Study medication was given in a single capsule, taken once per day. For the first two weeks after enrollment, the combination-therapy group and the group given folic acid and vitamin B_{12} received a loading dose of 5 mg of folic acid per day, whereas the other two groups received placebo for the first two weeks. Capsule formulations were manufactured (Alpharma) to be indistinguishable by color, weight, or their ability to dissolve in water.

The randomization was performed in blocks of 20 by Alpharma. Each study center received whole blocks of study medication and assigned it to patients in numerical order. All study personnel and participants were unaware of the treatment assignments.

Participants were given standard post–myocardial infarction therapy and were seen at a follow-up visit at 2 months and at a final visit after 2.0 to 3.5 years. Every six months after enrollment, study medication and a questionnaire were mailed to the participants. They were asked about study outcomes, compliance, and adverse effects. Those who did not return the questionnaire were interviewed by telephone by study personnel, or records were consulted to determine their vital status. Staff members at the coordinating center visited all participating hospitals to monitor data quality. Smerud Medical Research, on behalf of the Norwegian Research Council, conducted an audit of the trial and approved it.

Blood samples were obtained from all available participants at baseline, at two months, and at the final visit for the measurement of plasma total homocysteine, serum folate, and serum cobalamin. Levels of these vitamins were determined with the use of published methods.[19-22]

DEFINITION AND ASCERTAINMENT OF END POINTS

The primary end point was a composite of new nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, and sudden death attributed to CHD. Patients who were resuscitated after cardiac arrest were included in the analysis of the primary end point, whereas those with a silent myocardial infarction were not. For each participant, only the first of all such events was included in the analysis of the primary end point. If death occurred within 28 days after the onset of an event, the event was classified as fatal.

Secondary end points were myocardial infarction, unstable angina pectoris requiring hospitalization, coronary revascularization with percutaneous coronary intervention or coronary-artery bypass grafting, stroke, and death from any cause. Incident cases of cancer were recorded as a measure of safety.

Acute coronary events were categorized according to symptoms, new changes on electrocardiography, and levels of cardiac biomarkers. An unequivocal global or focal neurologic deficit that occurred suddenly and lasted more than 24 hours was required for the diagnosis of stroke. A detailed description of the end-point definitions of myocardial infarction, unstable angina pectoris, and stroke is available in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

All end points were adjudicated by members of the end-points committee, who were unaware of patients' treatment assignments. Data on possible events were collected at the hospitals by study nurses, who filled in forms and submitted relevant discharge letters and medical-record notes. For deaths that occurred outside the hospital, a copy of the death certificate was retrieved from the Causes of Death Registry. If deemed necessary by the end-points committee, additional information on the death was requested from the physician in charge. We obtained information on incident cancer (except basal-cell skin cancer) by using the Norwegian unique 11-digit person-number for each patient to search the National Cancer Registry. Patients completed forms every six months providing information on specified cardiovascular events. Finally, the study nurses filled in a questionnaire at the last follow-up visit.

STATISTICAL ANALYSIS

The calculation of the sample size was based on data from previous Scandinavian trials, assuming the three-year rate of the primary end point would be 25 percent in the placebo group. The planned enrollment of 3500 patients, with an average follow-up of 3.0 years, was expected to result in 750 primary events and give the study a statistical power of more than 90 percent to detect a 20 percent relative reduction in the rate of the primary end point, given a two-sided alpha value of 0.05.

The progress of the trial was monitored by the data and safety monitoring board. Because the incidence of the primary end point in the study group as a whole was lower than expected, the executive committee decided in March 2001 to extend the follow-up for those enrolled before June 30, 2001, to 3.5 years; to increase the total enrollment by 250 patients; and to follow those enrolled after June 30, 2001, until the date of their exit assessment, to be conducted between January 1 and March 31, 2004.

A chi-square value of more than 9 (corresponding to a P value of approximately 0.003) for the difference in mortality rates between treatment regimens was used to guide a decision to stop the study earlier than planned. The data and safety monitoring board evaluated the mortality rates after about 250 and 500 primary events had occurred, recommending that the trial should continue.

All analyses were conducted according to the intention-to-treat principle. The main focus was on comparison of treatment with folic acid and vitamin B_{12} with control (the combination-therapy group and the group given folic acid and vitamin B_{12} vs. the vitamin B_6 and placebo groups) and comparison of treatment with vitamin B_6 with control (the combination-therapy group and the group given vitamin B_6 vs. the group given folic acid and vitamin B_{12} and the placebo group). The factorial design also allowed a comparison of the combination-therapy group with the placebo group. Estimates of the hazard ratios and 95 percent confidence intervals were obtained with the use of Cox proportional-hazards models. Interactions were identified by applying the likelihood-ratio test to models with the interaction term and those without the interaction term and comparing the result. Kaplan–Meier survival analysis was used to compare the cumulative incidence of the primary end point in the four groups. Differences between groups in baseline characteristics were tested with analysis of variance. Study center was included as a covariate in all analyses. The reported P values are two-sided and are not adjusted for multiple comparisons.

Table 1. Baseline Characteristics of the Patients and Use of Concomitant Medications.*

Characteristic	Folic Acid, B_{12}, and B_6 (N=937)	Folic Acid and B_{12} (N=935)	B_6 (N=934)	Placebo (N=943)	P Value
Age — yr	63.6±11.9	63.2±11.6	62.5±11.7	62.6±11.4	0.11
Male sex — no. (%)	684 (73)	696 (74)	686 (73)	705 (75)	0.80
Total cholesterol — mmol/liter	5.8±1.2	5.8±1.2	5.8±1.3	5.7±1.3	0.49
Creatinine — μmol/liter	91±27	91±26	90±25	91±24	0.57
Systolic blood pressure — mm Hg	126±21	126±20	125±20	125±20	0.27
Diastolic blood pressure — mm Hg	73±13	73±13	72±13	72±13	0.25
Body-mass index†	26.5±4.0	26.2±3.5	26.3±3.8	26.3±3.8	0.66
Medical history — no. (%)					
Myocardial infarction	171 (18)	155 (17)	149 (16)	153 (16)	0.54
Angina pectoris	262 (28)	225 (24)	243 (26)	240 (26)	0.28
Stroke	50 (5)	36 (4)	38 (4)	33 (3)	0.21
Diabetes mellitus	103 (11)	83 (9)	86 (9)	96 (10)	0.40
Coronary-artery bypass surgery	55 (6)	40 (4)	38 (4)	44 (5)	0.26
Percutaneous coronary intervention	44 (5)	45 (5)	43 (5)	49 (5)	0.94
Receiving treatment for hypertension — no. (%)	281 (30)	250 (27)	268 (29)	275 (29)	0.46
Current smoker — no. (%)	429 (46)	405 (43)	460 (49)	453 (48)	0.05
Use of vitamin supplements — no./total no. (%)	271/931 (29)	275/930 (30)	257/928 (28)	263/935 (28)	0.78
Qualifying myocardial infarction					
Received primary or rescue PCI — no.(%)	59 (6)	61 (7)	54 (6)	54 (6)	0.86
Received thrombolysis — no./total no. (%)	383/932 (41)	403/931 (43)	405/929 (44)	381/942 (40)	0.42
Q-wave — no./total no. (%)	403/906 (44)	420/906 (46)	411/894 (46)	417/904 (46)	0.85
Peak creatine kinase — U/liter‡					
Median	969	1043	1004	929	0.62
Interquartile range	425–2156	461–2136	489–2084	457–2095	
Concomitant medication — no./total no. (%)					
Acetylsalicylic acid	757/874 (87)	789/880 (90)	764/853 (90)	778/880 (88)	0.16
Beta-blockers	797/873 (91)	808/879 (92)	768/853 (90)	802/881 (91)	0.58
Statins	690/873 (79)	721/879 (82)	704/856 (82)	712/880 (81)	0.30
ACE inhibitors	283/868 (33)	264/875 (30)	263/851 (31)	262/880 (30)	0.59
Angiotensin II–receptor antagonists	38/866 (4)	46/873 (5)	37/849 (4)	48/879 (6)	0.60
Diuretics	162/869 (19)	153/874 (18)	147/851 (17)	152/879 (17)	0.86
Warfarin	123/868 (14)	89/873 (10)	88/851 (10)	104/879 (12)	0.04

* Plus–minus values are means ±SD. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for creatinine to milligrams per deciliter, divide by 88.4. PCI denotes percutaneous coronary intervention, and ACE angiotensin-converting enzyme.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Information was available on 673 patients in the combination-therapy group, 678 in the group given folic acid and vitamin B_{12}, 671 in the group given vitamin B_6, and 669 in the placebo group.

RESULTS

Between December 12, 1998, and March 31, 2002, 3749 patients were enrolled in the trial at 35 Norwegian hospitals and assigned to one of the four treatment groups. The four groups were well balanced with regard to baseline characteristics, prognostic factors, and concomitant medications (Table 1).

The mean length of follow-up was 36 months (median, 40). Five participants withdrew their informed consent and did not receive the assigned treatment, and 404 (11 percent) stopped taking study medication during the trial. The percentages stopping treatment were similar in the four study groups. A total of 94 percent of all surviving patients attended the final visit. Outcomes among those who did not attend the final visit were assessed by examining relevant medical records and by direct contact. No patients were lost to follow-up in the mortality analysis, but a total of 20 (3 to 8 in each group) had incomplete follow-up data on nonfatal events.

COMPLIANCE AND SIDE EFFECTS

The questionnaires on compliance and side effects were returned by 99 percent, 94 percent, and 93 percent of the participants after one, two, and three years, respectively. The response rates were similar in the four treatment groups. About 98 percent of those who returned the questionnaire reported that they complied with the study protocol or had missed taking study medication only a few times. This percentage was similar in the four groups at one, two, and three years.

The participants were asked whether they had had adverse effects related to the study medication (yes or no). The percentages who responded "yes" were similar (18 to 24 percent) in the four treatment groups throughout the study. No serious adverse events were reported.

EFFECT OF INTERVENTION ON B VITAMIN STATUS

In the two groups that received folic acid and vitamin B_{12}, the mean total homocysteine level was reduced by a mean of 27 percent, from 13.0 μmol per liter (1.8 mg per liter) at baseline to 9.6 μmol per liter (1.3 mg per liter) at the end of the intervention (Table 2). Among those who received folic acid, the mean total homocysteine level was a mean of 4.2 μmol per liter (0.57 mg per liter) lower than the level in the group that did not receive folic acid after two months (a difference of 31

Table 2. Plasma Levels of Total Homocysteine and B Vitamins at Baseline, after Two Months, and at the End of the Intervention.*

Variable	Folic Acid, B_{12}, and B_6 (N=937)†	Folic Acid and B_{12} (N=935)‡	B_6 (N=934)§	Placebo (N=943)¶
Total homocysteine (μmol/liter)				
Baseline	13.1±5.0	12.9±4.3	13.3±6.1	13.2±5.2
2 Mo	9.4±3.0	9.5±2.8	13.7±5.7	13.7±5.6
End of intervention	9.5±3.6	9.8±4.0	13.3±5.4	13.6±6.2
Folate (nmol/liter)				
Baseline	13.1±27.5	11.7±28.4	9.4±6.6	9.6±6.0
2 Mo	59.9±29.5	68.2±30.0	7.9±7.1	9.9±6.3
End of intervention	61.8±31.7	70.4±36.4	10.4±9.6	13.1±14.5
Vitamin B_{12} (pmol/liter)				
Baseline	388±161	400±311	388±167	383±182
2 Mo	571±212	578±372	398±158	393±143
End of intervention	638±370	648±414	398±320	390±171

* Values are means ±SD. To convert values for homocysteine to millligrams per liter, divide by 7.396. To convert values for folate to nanograms per milliliter, divide by 2.266. To convert values for vitamin B_{12} to picograms per milliliter, divide by 0.7378.
† Blood samples were available from 935 patients at baseline, 855 at two months, and 750 at the end of the intervention.
‡ Blood samples were available from 933 patients at baseline, 849 at two months, and 770 at the end of the intervention.
§ Blood samples were available from 930 patients at baseline, 819 at two months, and 747 at the end of the intervention.
¶ Blood samples were available from 935 patients at baseline, 851 at two months, and 760 at the end of the intervention.

Table 3. Clinical Outcomes and Rate Ratios.

Variable	Total No.	Folic Acid, B_{12}, and B_6 (N=937)	Folic Acid and B_{12} (N=935)	B_6 (N=934)	Placebo (N=943)	Folic Acid and B_{12} vs. No Folic Acid and B_{12}*		B_6 vs. No B_6†		Folic Acid, B_{12}, and B_6 vs. Placebo‡	
		no. of cases (rate/1000 observation-yr)				Rate Ratio (95% CI)§	P Value	Rate Ratio (95% CI)§	P Value	Rate Ratio (95% CI)§	P Value
Primary end point¶	716	201 (81.6)	168 (66.9)	175 (70.1)	172 (67.2)	1.08 (0.93–1.25)	0.31	1.14 (0.98–1.32)	0.09	1.22 (1.00–1.50)	0.05
Myocardial infarction‖	643	182 (73.0)	147 (57.5)	161 (64.0)	153 (59.2)	1.06 (0.91–1.24)	0.47	1.17 (1.00–1.37)	0.05	1.23 (0.99–1.52)	0.06
Fatal**	235	68 (24.5)	47 (16.8)	61 (22.1)	59 (21.0)	0.96 (0.74–1.24)	0.75	1.24 (0.96–1.61)	0.10	1.19 (0.84–1.69)	0.34
Nonfatal	462	132 (53.0)	113 (44.2)	113 (44.9)	104 (40.2)	1.14 (0.95–1.37)	0.16	1.15 (0.96–1.38)	0.14	1.30 (1.00–1.68)	0.05
Stroke	98	21 (7.7)	28 (10.2)	22 (8.1)	27 (9.7)	1.02 (0.68–1.51)	0.94	0.81 (0.54–1.20)	0.29	0.83 (0.47–1.47)	0.52
Death from any cause	365	104 (37.5)	80 (28.7)	92 (33.4)	89 (31.7)	1.02 (0.83–1.26)	0.82	1.19 (0.96–1.46)	0.11	1.21 (0.91–1.61)	0.19
Hospitalization for unstable angina pectoris	488	125 (50.5)	126 (50.6)	105 (41.6)	132 (53.0)	1.06 (0.89–1.27)	0.50	0.88 (0.74–1.05)	0.17	0.93 (0.73–1.19)	0.57
Coronary-artery bypass surgery	584	138 (57.1)	139 (57.0)	150 (63.3)	157 (65.0)	0.90 (0.76–1.05)	0.18	0.99 (0.84–1.17)	0.91	0.89 (0.71–1.13)	0.34
Percutaneous coronary intervention	1096	257 (122.6)	270 (129.4)	279 (135.0)	290 (141.6)	0.92 (0.82–1.03)	0.16	0.94 (0.83–1.05)	0.27	0.86 (0.72–1.02)	0.08
Cancer	144	40 (15.5)	39 (14.9)	25 (9.8)	40 (15.2)	1.22 (0.88–1.70)	0.23	0.84 (0.60–1.16)	0.29	1.02 (0.65–1.58)	0.94

* The comparison is for the combination-therapy group and the group given folic acid and vitamin B_{12} with the group given vitamin B_6 and the placebo group.
† The comparison is for the combination-therapy group and the group given vitamin B_6 with the group given folic acid and vitamin B_{12} and the placebo group.
‡ The comparison is for the combination-therapy group with the placebo group.
§ Values were adjusted for study center. CI denotes confidence interval.
¶ The primary end point was a composite of nonfatal or fatal myocardial infarction (including sudden death attributed to coronary heart disease) and nonfatal or fatal stroke. Only the first event is included in the composite primary end point.
‖ If a participant first had a nonfatal myocardial infarction and then a fatal myocardial infarction, only the nonfatal myocardial infarction was included in the category of myocardial infarction.
** The category includes sudden death attributed to coronary heart disease.

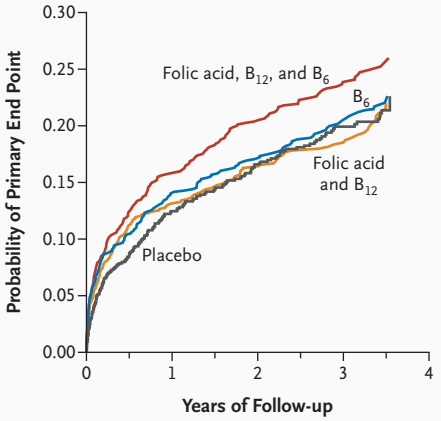
percent, P<0.001) and 3.8 μmol per liter (0.51 mg per liter) lower at the end of the intervention (a difference of 28 percent, P<0.001). The mean total homocysteine level did not change significantly in the group treated with vitamin B_6 alone. Treatment with folic acid and vitamin B_{12} led to significant increases, by a factor of 5 to 6, in the mean levels of plasma folate and increases in plasma vitamin B_{12} by approximately 60 percent.

CLINICAL END POINTS

Table 3 shows the number of primary and secondary end points and event rates in the treatment groups and the rate ratios. Treatment with folic acid in combination with vitamin B_{12} — with or without vitamin B_6 — did not significantly reduce the risk of the primary end point, as compared with placebo. Both treatment regimens were associated with a nonsignificant increase in risk, mainly driven by an event rate that was 22 percent higher in the combination-therapy group than in the placebo group (P=0.05). Figure 1 shows Kaplan–Meier curves of the event rates for the primary end point in the treatment groups. The cumulative hazard ratio for the combination-therapy group, as compared with the other three groups, was 1.20 (95 percent confidence interval, 1.02 to 1.41; P=0.03). Adjusting for the use of warfarin at baseline (which differed among the four groups, as shown in Table 1) did not alter the rate ratios significantly.

The risk of the secondary end points was not significantly influenced by treatment with folic acid and vitamin B_{12}. Vitamin B_6 therapy was associated with a 17 percent increase in the risk of myocardial infarction (P=0.05), and combination therapy was associated with a 30 percent increase in the risk of nonfatal myocardial infarction (P=0.05) (Table 3). Given, however, that these analyses were not adjusted for multiple comparisons, these apparent associations could readily be explained by chance. There was a numerical increase in the risk of cancer among patients assigned to folic acid, but this difference was not significant (Table 3).

Subgroup analyses of the primary end point are shown in Table 4. Treatment with B vitamins was not associated with a significant benefit in any subgroup. An increased risk associated with treatment was observed among patients with higher baseline levels of total homocysteine (more than 13 μmol per liter, vs. 13 μmol per liter or less) who received combination therapy (P=0.04) and among those with a myocardial infarction without ST-segment elevation who received folic acid and vitamin B_{12} (P=0.04).



No. at Risk

Folic acid, B_{12}, and B_6	937	795	745	517
Folic acid and B_{12}	935	812	764	518
B_6	934	805	766	511
Placebo	943	823	771	523

Figure 1. Kaplan–Meier Estimates of the Probability of Reaching the Primary End Point during Follow-up.

The primary end point was a composite of fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and sudden death attributed to coronary heart disease.

The baseline level of total homocysteine was a significant predictor of the primary end point (relative risk associated with a 3-μmol difference in the total homocysteine level, 1.05; 95 percent confidence interval, 1.01 to 1.09; P=0.01) after adjustment for study center, age, sex, systolic blood pressure, total cholesterol level, and smoking status. After additional adjustment for the creatinine level, the relative risk was 1.03 (P=0.10).

DISCUSSION

We did not find that secondary intervention with folic acid (plus vitamin B_{12}) and vitamin B_6, alone or in combination, decreased the risk of complications and death from cardiovascular causes among patients with a recent myocardial infarction, despite a substantial reduction in plasma total homocysteine levels in patients receiving folic acid. Contrary to expectations, there was a trend

Table 4. Rate Ratios for the Primary End Point in Various Subgroups.*

Characteristic	Total No.	Folic Acid and B_{12} vs. No Folic Acid and B_{12}†	B_6 vs. No B_6‡	Folic Acid, B_{12}, and B_6 vs. Placebo§
		rate ratio (95% confidence interval)		
Sex				
Male	2771	1.06 (0.89–1.27)	1.14 (0.96–1.36)	1.23 (0.96–1.57)
Female	978	1.07 (0.82–1.41)	1.11 (0.85–1.46)	1.10 (0.75–1.61)
Age				
≤65 yr	2068	1.17 (0.92–1.51)	1.11 (0.87–1.42)	1.26 (0.89–1.80)
>65 yr	1681	0.97 (0.80–1.16)	1.12 (0.93–1.34)	1.05 (0.81–1.36)
Total homocysteine				
≤13 μmol/liter	2237	0.97 (0.79–1.20)	1.03 (0.84–1.27)	1.02 (0.75–1.37)
>13 μmol/liter	1496	1.27 (1.02–1.66)	1.26 (1.02–1.55)	1.56 (1.16–2.09)
Creatinine				
≤100 μmol/liter	2845	1.05 (0.88–1.25)	1.04 (0.87–1.25)	1.09 (0.85–1.46)
>100 μmol/liter	891	1.13 (0.87–1.47)	1.32 (1.01–1.71)	1.44 (0.98–2.11)
History of CVD or diabetes¶				
No	1641	1.28 (0.95–1.73)	0.92 (0.68–1.24)	1.15 (0.76–1.75)
Yes	2108	1.04 (0.88–1.23)	1.22 (1.03–1.45)	1.28 (1.01–1.62)
Current smoker				
No	2002	1.08 (0.90–1.30)	1.06 (0.88–1.27)	1.12 (0.86–1.45)
Yes	1747	1.04 (0.81–1.32)	1.28 (1.01–1.63)	1.34 (0.95–1.88)
Qualifying myocardial infarction				
No ST-segment elevation	1959	1.25 (1.03–1.51)	1.12 (0.92–1.35)	1.40 (1.07–1.82)
ST-segment elevation	1651	0.90 (0.71–1.15)	1.11 (0.87–1.41)	1.07 (0.76–1.51)

* Values were adjusted for study center. Information on total homocysteine was available for 3733 patients, information on creatinine was available for 3736 patients, and information on ST-segment elevation was available for 3610 patients. To convert values for homocysteine to milligrams per liter, divide by 7.396. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586.

† The comparison is for the combination-therapy group and the group given folic acid and vitamin B_{12} with the group given vitamin B_6 and the placebo group.

‡ The comparison is for the combination-therapy group and the group given vitamin B_6 with the group given folic acid and vitamin B_{12} and the placebo group.

§ The comparison is for the combination-therapy group with the placebo group.

¶ CVD denotes cardiovascular disease (i.e., myocardial infarction, angina pectoris, stroke, coronary-artery bypass surgery, or percutaneous coronary intervention).

toward an increased rate of events among patients receiving B vitamins, in particular the combination of folic acid, vitamin B_6, and vitamin B_{12}.

Noncompliance is not a likely explanation for these negative findings, because the high rate of compliance, although probably overreported, was corroborated by a biochemical assessment of vitamin status. The power of the trial was slightly less than planned. However, it had a power of 0.80 to detect an 18 percent reduction in the risk of the primary end point and a power of 0.87 to detect the prespecified, hypothesized 20 percent reduction in risk with vitamin therapy.

Our trial was large and included patients from community and referral hospitals in different regions of Norway; we used liberal entry criteria to increase the generalizability of the results, and the baseline characteristics of NORVIT participants were similar to those of patients with acute myocardial infarction who have participated in recent trials conducted worldwide.[23] We therefore believe our results are applicable to the majority of patients who present with acute myocardial infarction.

Many observational studies have demonstrated that the plasma total homocysteine level is a

predictor of cardiovascular events[1] in the general population[2] as well as in patients with a diagnosis of cardiovascular disease,[3] but no causative role of homocysteine has been substantiated by the results of intervention trials involving homocysteine-reducing treatment. Results from a large secondary intervention trial[15] and three smaller studies[24-26] suggest that treatment with B vitamins has no effect on stroke recurrence or on complications and death from cardiovascular causes. Similar findings were noted in the Heart Outcomes Prevention Evaluation (HOPE) 2 trial of B vitamin therapy in high-risk patients, which is reported elsewhere in this issue of the *Journal*.[27]

Folic acid in combination with vitamin B_6 may reduce the rate of restenosis in patients undergoing coronary balloon angioplasty,[17] but it may increase the rate after coronary stenting.[18] The latter finding came from a study that used a dose of B vitamins similar to that of the combination therapy in our study, and the results resemble our findings of increased event rates among patients receiving folic acid plus a high dose of vitamin B_6. Thus, secondary intervention trials with high doses of B vitamins in patients with cardiovascular disease have mostly shown no effect, not unlike the failure to prevent heart disease with high doses of single nutrients like vitamins E, C, and A. These findings should encourage trials with physiologic and more balanced doses of micronutrients.[28]

The effects of folate and homocysteine-lowering therapy have been evaluated with the use of cardiovascular surrogate markers, including endothelium-dependent vascular reactivity and markers of vascular dysfunction and inflammation. Improved function has been demonstrated in some[8,29-32] but not all[33-38] studies. The lack of benefit of homocysteine-lowering therapy in the clinical setting suggests that such treatment may have effects that promote atherothrombosis. Folic acid may affect endothelial function[8] and support cell growth through mechanisms that are independent of homocysteine.[39] Increased proliferation of vascular smooth-muscle cells and matrix formation have been suggested as possible mechanisms behind the increased risk of in-stent restenosis in patients given folic acid and vitamin B_6.[18] Furthermore, vitamin B_6 is involved in numerous enzymatic reactions and biologic functions, including cell growth, immunocompetence, and cholesterol metabolism,[40] and high levels may inhibit angiogenesis.[41] Conceivably, high doses of vitamin B_6 may adversely affect vascular remodeling and myocardial repair, leading to increased rates of complications and death among patients with cardiovascular disease.

In summary, the NORVIT trial demonstrated that intervention with folic acid, with or without high doses of vitamin B_6, did not lower the risk of recurrent cardiovascular disease or death after an acute myocardial infarction. Such therapy may even be harmful after acute myocardial infarction or coronary stenting[18] and should therefore not be recommended.

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Dr. Ueland reports having received consulting fees from Nycomed and is a member of the steering board of both the nonprofit Foundation to Promote Research into Functional Vitamin B_{12} Deficiency and Bevital, a company owned by the foundation. A provisional application (62924 [52365]) for a patent entitled "Determination of folate in fresh and stored serum or plasma as paraaminobenzoylglutamate" was filed on March 4, 2005; Dr. Ueland is listed as one of the inventors. The patent is owned by Bevital. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The following investigators and institutions, all in Norway, participated in the NORVIT trial: **Investigators** (listed in descending order of the number of randomized patients, with the number of patients shown in parentheses) — *Sentralsykehuset i Akershus, Nordbyhagen* (357): J. Eriksen, I. Sletten Løvik, G. Hofset, U. Hågensen; *Universitetssykehuset Nord-Norge, Tromsø* (339): F. Saleh, H. Wang, W. Gamst, J. Aarsland, F. Johnsen; *Vest-Agder sentralsykehus, Kristiansand* (275): F.T. Gjestvang, G. Eidvinsson, S.H. Schou; *Sentralsykehuset i Møre og Romsdal, Aalesund* (206): T. Hole, Ø. Kaarbøe, L. Gjerde, L. Walderhaug; *Buskerud sentralsykehus, Drammen* (200): S. Ritland, B. Aakervik, MG. Ødegaard, I. Mikalsen, E.-M. Christiansen; *Sentralsjukehuset i Hedmark, Hamar* (194): K. Andersen, M. Ekelund Thørud, T.K. Dalsbakken; *Nordland sentralsykehus, Bodø* (191): K.T. Lappegård, A. Sivertsen, B. Tegnander, J.H. Flage, V. Andreasson, L. Stolpen; *St. Olav's Hospital, Universitetsklinikken i Trondheim, Trondheim* (175): J.D. Solli, H. Thürmer, F. Alstad Berg, S. Holst; *Lovisenberg Diakonale sykehus, Oslo* (147): K.A. Langerød, G. Vollan; *Hammerfest sykehus, Hammerfest* (137): S. Høybjør, B. Rystad, R. Hjertø; *Kongsvinger sykehus, Kongsvinger* (133): J. Aaseth, E. Melbye; *Harstad sykehus, Harstad* (115): K. Hofsøy, A. Karlsen; *Fylkessjukehuset på Voss, Voss* (115): F. Bergo, G.-O. Nedreberg; *Kongsberg sykehus, Kongsberg* (106): K. Berget, A. Sagosen, A. Fulsebakk, N. Wangestad; *Oppland sentralsykehus, Gjøvik* (106): I. Stokland, P.

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