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‡	
						Rate Ratio (95% CI)§	P Value	Rate Ratio (95% CI)§	P Value	Rate Ratio (95% CI)§	P Value
		no. of cases (rate/1000 observation-yr)									
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.

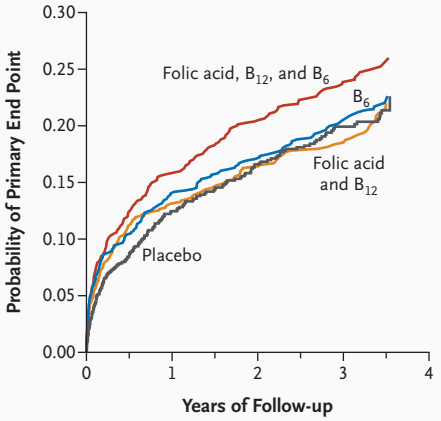
percent, P<0.001) and 3.8 μmol per liter (0.51 mg per liter) lower at the end of the intervention (a difference of 28 percent, P<0.001). The mean total homocysteine level did not change significantly in the group treated with vitamin B_6 alone. Treatment with folic acid and vitamin B_{12} led to significant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

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Electronic Supplementary Appendix

End point classifications, end point definitions, and diagnostic criteria in the *NORVIT* trial

Participants are followed for the occurrence of each type of event listed in the following classification scheme, occurring between the date of inclusion and end of follow-up for the participant in question.

End point classification

Primary end point

is a composite of the following codes:
1.1.1 - 1.1.5, 2.1.1 - 2.1.2, 2.2.0, 1.3.2 - 1.3.4, 2.5.2 - 2.5.4

A participant may experience several events of the composite end point during follow-up. In the Cox regression and Kaplan-Meier analyses, time to the first event of all primary end point codes is calculated for each participant.

Secondary end points

1. Death from all causes: 1.1.1 – 1.9.0

2. Coronary events
   - Fatal myocardial infarction: 1.1.1 – 1.1.5
   - Non-fatal myocardial infarction: 2.1.1 – 2.1.2, 2.2.0
   - Hospitalized unstable angina pectoris: 2.3.1
   - Coronary artery bypass surgery: 2.4.1
   - Percutaneous coronary intervention: 2.4.2

3. Fatal and non-fatal stroke
   - 1.3.2 – 1.3.4 and 2.5.2 – 2.5.4

End point definitions and diagnostic criteria

1. Fatal events

Deaths are classified by the End point committee in the following subgroups:

1.1 Coronary deaths

1.1.1 Death within 28 days from the onset of symptoms of a definite myocardial infarction (MI); the event verified as definite MI according to NORVIT criteria (Appendix 1), or autopsy confirming either a recent MI or a recent occluding coronary thrombus.

1.1.2 Death within 28 days from the onset of symptoms of a probable myocardial infarction; with the event classified as a probable MI according to NORVIT criteria (Appendix 1), or autopsy confirming probable MI.

1.1.3 Death after the onset of chest pain, syncope, acute pulmonary edema, or cardiogenic shock without confirmed MI (death occurring during hospital stay for the index event: see code 1.1.5)

1.1.4 Sudden, unexpected death, witnessed or unwitnessed, when there is no reason to presume another cause of death (excluded are patients with sign or symptoms of other fatal disease when the subject was last observed alive); deaths without any information of symptoms; or instantaneous death.

1.1.5 Death from ventricular arrhythmia, pulmonary edema, or sudden, unexpected death, occurring during the hospital stay for the index MI, when there is no confirmative evidence for a new MI.

1.1.6 Death from MI related to a coronary invasive procedure or surgery.

1.2.0 Other cardiac disease, i.e. death from non-coronary heart disease.(examples: myocarditis, primary arrhythmia, valvular disease)

1.3 Cerebrovascular deaths

Death within 28 days after the onset of symptoms of stroke. Stroke is classified in the following subgroups according to the NORVIT criteria (Appendix 2).

1.3.1 Subarachnoidal hemorrhage
1.3.2 Cerebral infarction
1.3.3 Intracerebral hemorrhage
1.3.4 Unspecified stroke
1.3.5. Death from stroke related to a surgical or invasive procedure

For subgroups 1.3.2 - 1.3.4, symptoms (neurological deficits) must have been present for 24 hours or until death occurred.
If information on symptoms and clinical findings is missing, the diagnosis should be based on autopsy results.

1.4.0 Death from aortic aneurysm.
Dissecting/ruptured aneurysm

1.5 Death from pulmonary embolism.

1.5.1 Pulmonary embolism confirmed by scintigraphy, CT, angiography, or autopsy results, regardless whether the diagnosis had been clinically detected or not.
1.5.2 Pulmonary embolism clinically diagnosed, without test results to confirm the diagnosis.

1.6.0 Death from other cardiovascular disease

1.7.0 Death from malignant disease

1.8.0 Violent death: suicide, murder, accident

1.9.0 Death from other causes

2. Non-fatal events

2.1 Myocardial infarction

2.1.1 Definite MI

a) Typical, atypical or inadequately described symptoms (category 1, 2 or 5) + ECG in category 2
or:
b) Typical symptoms (category 1) + MI biomarker in category 1 or 7, regardless of ECG
or:
c) Atypical or inadequately described symptoms (category 2 or 5) + MI biomarker in category 1 or 7 + ECG in category 3

2.1.2 Probable MI

a) Typical symptoms (category 1) + MI biomarker in category 2 + ECG in category 3
or:
b) Typical symptoms (category 1) + MI biomarker in category 2 + ECG in category 4 or 9
or:
c) Atypical or inadequately described symptoms (category 2 or 5) + MI biomarker in category 2 + ECG in category 3
d) Atypical or inadequately described symptoms (category 2 or 5) + MI biomarker in category 1 or 7 + ECG in category 4 or 9

2.1.3 Silent MI

This code is used only for new silent Q-infarctions diagnosed from routine ECG during follow-up and at the latest by the end of follow-up, as compared with an ECG recorded earlier during follow-up, but after the inclusion in the trial. Clinicians at local hospitals will make the diagnosis.

2.1.4 MI related to a procedure

Includes cases of MI biomarkers in category 1, 2 or 7 appearing not later than the day after an invasive procedure, regardless of cECG and symptom classifications.

2.2.0 Cardiac arrest with successful resuscitation

Includes cases where a definite or probable MI could not be confirmed
(for example because cardioversion was performed)

2.3 Acute coronary events that do not satisfy criteria in category 2.1.1 - 2.2.0:

2.3.1 Hospitalized acute episode of angina pectoris

Includes:
a) Prolonged chest pain
Duration 20 minutes or more, without dynamic ECG-changes or biomarker changes as in definite or probable MI (for example unstable angina)
b) Ischemic episode
Chest pain (one or more episodes, each one < 20 minutes), with either equivocal ECG-changes or non-specifically increased biomarkers, that together do not satisfy the criteria of definite or probable MI.

2.3.2 Acute left ventricular failure, triggered by an ischemic episode

2.3.3 Acute left ventricular failure, not triggered by an ischemic episode

2.4 Revascularizations

will be coded as secondary end points regardless of whether or not they occur in conjunction with another event. Deaths, acute MIs, and strokes that occur within 28 days after CABG/PTCA/carotid surgery will be classified as end points in the respective subgroups.

2.4.1 CABG
2.4.2 PTCA and coronary endarterectomy.
First PTCA after the index MI, including unsuccessful attempts of PTCA
2.4.3 Recurrent PTCA, including unsuccesful attempts of PTCA
2.4.4 Carotid endarterectomy
2.4.5 TPA of other arteries

2.5. Non-fatal stroke

Rapid development of clinical signs of focal or global* disturbance of cerebral function lasting more than 24 hours, and without evidence of a non-vascular cause.
If symptoms last < 24 hours, the diagnosis will be TIA.

* global refers to subarachnoidal hemorrhage and to comatous patients

2.5.1 Subarachnoidal hemorrhage
2.5.2 Cerebral infarction
2.5.3 Intracerebral hemorrhage
2.5.4 Unspecified stroke
2.5.5 TIA
2.5.6 Stroke related to a surgical or invasive procedure

See Appendix for subgroup diagnostic criteria

2.6.0 Aortic aneurysm, which must be:
a) symptomatic
b) operated upon, or
c) surgery is indicated (i.e. cases in which there are contraindications against surgery)
A broadened aortic artery accidentally detected at ultrasound, X-ray or during surgery for another condition, does not satisfy the criteria.

2.7.0 Pulmonary edema
Must have been detected by scintigraphy, angiography, CT or MRI.

2.8.0 Deep vein thrombosis
Must have been detected by ultrasound or venography. A swollen leg or arm is not sufficient to make this diagnosis

2.9.0 Cancer
NORVIT will apply for a linkage to the Cancer Registry to detect incident cases of cancer

2.9.1 Ventricular arrhythmia (not in conjunction with an acute MI)

2.9.2 Atrial fibrillation /flutter (not in conjunction with an acute MI)

2.9.3 Hospitalizations for chest pain and similar symptoms that cannot be classified in code 2.3.1

2.9.4 Hospitalization for cardiovascular investigations, transferral from another hospital in connection with a cardiovascular event, and similar hospitalizations.

APPENDIX 1

Diagnostic criteria; CORONARY EVENTS

1. Symptoms

Codes:

1 Typical
2 Atypical
3 Other
4 None
5 Inadequately described
9 Insufficient information

Code 1: Typical symptoms are
central (retrosternal) chest pain lasting 20 minutes or until pain relief is given, and which is not definitely due to non-cardiological causes. The pain may radiate to jaw, arms, abdomen, back, shoulder. “Ache” ,“discomfort”, “pressure” are synonyms for pain.

Symptoms registered for a coronary event apply to a period of 28 days following the onset. If more than one episode occurs during this interval, the lowest symptom category will be coded. Example: Code= 1 if typical pain occurred on day 5, while atypical symptoms occurred on day 1. The date of event is nevertheless day 1, when the symptoms caused a medical consultation.

If symptoms are typical, but duration is not stated, category 5 should be used. If words like "prolonged", "longlasting" are used, or if it is evident from the context that pain must have lasted for more than 20 minutes, category 1 should be used.

Typical chest pain leading to syncope, shock or pulmonary edema, is coded as category 1 even if unconsciouosness/death occurs within 20 minutes.

Code 2: Atypical symptoms are
- atypical pain
- acute left ventricular failure, in the absence of typical symptoms
- cardiogenic shock, in the absence of typical symptoms
- syncope, in the absence of typical symptoms

AND absence of other heart disease AND no evident non-cardiac cause

Atypical pain may be pain attacks of short duration, or pain in arms, jaw, or abdomen, without concurrent chest pain.

Code 3: To be used in cases of adequate description of symptoms that do not satisfy code 1 or 2 , and for symptoms due to a defined non-cardiac cause or non-atherosclerotic heart disease (pericarditis)

Code 4: To be used in cases of non-fatal events where the patient did not report any symptoms, or in fatal cases where eye witnesses did not sense that the patient had any symptoms before death occurred (instantaneous death)

Code 5: To be used in cases of typical pain of non-defined duration, precluding the use of code 1

Code 9: To be used if information is inadequate for any other code

2. MI biomarkers in serum

Codes:

1	Very much elevated MI biomarkers
2	Moderately elevated MI biomarkers
3	Non-specifically elevated MI biomarkers
4	Normal MI biomarkers
5	Inadequate serum sampling
6	Troponin I or CK-MB slightly elevated (”gray zone”)
7	Troponin I between diagnostic cut-off value and 2 x diagnostic cut-off value
9	Insufficient data for other codes

Code 1: Serial change of enzymes, at least one reading ≥2 x upper reference limit when measured within 72 hours after the onset of symptoms, hospitalization, or after a new episode during the 28-days interval from the original date of onset.
Code 2: Serial change of enzymes, but all readings < 2 x upper reference limit, measured within 72 hours after the onset of symptoms.
Code 3: Very much elevated (≥2x) serum-enzymes, but no normalizing, or the elevation may be due to another disease, defibrillation, or surgery, or less than 3 weeks since index MI ; however, if suspected recurrent MI: new, acute elevation of troponin of at least 50% in the post MI recovery-phase is coded in category 1 or 2, dependent on the magnitude of elevation.
Code 4: To be used when enzyme test was taken during relevant time interval, was adequately reported, and was within the reference range.
Code 5: To be used when enzyme test has been taken, but not within the 72 hours interval after the onset of symptoms.
C*ode 6*: Troponin I between upper reference value and diagnostic cut-off value.
(when only troponin has been analysed, or if all other biomarkers were within reference range)
Code 7: Troponin I between diagnostic cut-off value and 2 x diagnostic cut-off value.
Code 9: To be used when enzyme test has not been done, and when analysis results are unavailable.

Troponin I is classified as:
Code1: Elevated: ≥ 2 x diagnostic cut-off value
Code 4: Normal: 0.0 – upper reference value
Code 6: “Gray zone” : Upper reference value – diagnostic cut off for Troponin I (and CK-MB when the laboratory uses such a classification)
Code 7: Slightly elevated: between diagnostic cut off value and 2 x diagnostic cut off value

In those cases when the laboratory in charge did not set a diagnostic cut off value for Troponin I, the value 2.0 is to be used.
No laboratory has stated a diagnostic cut-off value for Troponin T, and therefore Troponin T follows regular classification scheme for enzymes.

Hierarchy between troponin and other MI biomarkers:

1. If troponin is the only MI biomarker used: highest reading to be coded.

2. If troponin and other markers are analysed. Troponin and CK-MB are equal, highest maximum reading of the two is coded even if the other biomarker is within reference range.
3. Highest reading of Troponin or CK-MB to be coded regardless of whether CK is elevated or is within reference range.
4. Maximum CK reading to be coded if neither CK-MB nor Troponin has been analysed.
5. ASAT (SGOT) value to be coded only if no other, and more relevant biomarker has been analysed.

3. ECG criteria

Codes:

1	Silent MI as defined by ECG
2	Definite new MI as defined by ECG
3	Possible new MI as defined by ECG
4	Other ECG findings, inclusive of normal ECG
5	Uncodable ECG
7	Atrial fibrillation
9	ECG not available

Code 1: Silent MI
Routine ECG shows a pathological Q-wave , width $\geq$ 0.04 sec and amplitude $\geq$ 25% of the following R-wave amplitude, appearing after a EKG recorded earlier during follow-up, and after the inclusion in the trial.

Code 2: Definite new MI

2.1 No pathological Q-wave on admission; development of pathological Q-wave, width $\geq$ 0.04 sec and amplitude $\geq$ 25% of R-wave amplitude.

2.2 Definite pathological Q-wave present on admission + sequential development of ST-T changes and/or sequential development of persisting negative T-wave.

Code 3: Possible new MI

3.1 New Q-wave, but Q-width < 0.04 sec and/or Q-amplitude < 25% of R-wave amplitude.

3.2 New or sequential development of ST-T changes in one or more leads:
In anterior leads $\geq$ 1mm; in inferior leads $\geq$ 0.5 mm as compared to the isoelectrical line.

3.3 New or sequential development of persisting negative T-wave in one or more lead, regardless of size of deviation from isoelectrical line.

Code 4: Normal ECG:
No or unspecified changes in ECG.

Code 5: ECG cannot be coded for technical reasons or because of suppression codes (bundle branch block)

Code 9: ECG was not recorded or is unavailable.

4. Autopsy results

Code 1: Definite MI
Signs of acute MI and/or fresh occluding thrombus in coronary vessels apparent for the pathologist at the autopsy. Old MI changes may be present.
Code 2: Old MI.
Code 3: New cerebral infarction.
Code 4: New intracerebral hemorrhage.
Code 5: Autopsy not performed.
Code 6. Old cerebral infarction or old intracerebral hemorrhage.
Code 7. No sign of myocardial infarction or cerebral stroke.
Code 9: Information is missing whether or not autopsy was performed, or autopsy results are unavailable

5. Thrombolysis

During a hospital stay because of MI
Code 1. Streptokinase (Streptase) or non-specified thrombolytic drug
C*ode 2*: Alteplase (Actilyse)
Code 3. Reteplase (Rapilysin)
Code 5: No thrombolytic treatment
Code 9: Insufficient information whether thrombolytic treatment was given or not

6. Stress –ECG (A-ECG)

In conjunction with code 2.3.1: A-ECG performed in connection with the relevant event (i.e. during the hospital stay)
Code 1. Negative A-ECG
Code 2: Negative A-ECG, submaximal exertion
Code 3: Inconclusive A-ECG
Code 4: Positive A-ECG (coronary chest pain or ischemic ECG-changes)
Code 5: A-EKG not performed
Code 9: Insufficient information whether A-ECG was performed or not

APPENDIX 2

Diagnostic criteria for STROKE

Rapid development of clinical signs of focal or global* disturbance of cerebral function of more than 24 hours duration, or death occurring before 24 hours, and without any suspicion of a non-vascular cause. If duration of otherwise typical symptoms < 24 hours, the diagnosis will be TIA.

* refers to subarachnoidal hemorrhage and to unconcscious patients

Diagnostic criteria for subgroups of stroke:

1.3.1 /2.5.1 Subarachnoidal hemorrhage
Diagnosis based on symptoms, clinical neurological findings and CT, MRI (or cerebral angiography) (4S…." and CT, MR or spinal fluid analysis"), or findings during surgery

1.3.2 / 2.5.2 Cerebral infarction
Diagnosis made in the absence of signs of hemorrhage at CT, MR or in spinal fluid.
No distinction is drawn between non-embolic and embolic cerebral infarction.

1.3.3 / 2.5.3 Intracerebral hemorrhage
Intracerebral hematoma detected by CT or MRI , with or without breakthrough bleeding in ventricles (blood in spinal fluid)

1.3.4 / 2.5.4 Unspecified stroke
Symptoms and neurological signs typical for stroke, but no additional investigations performed (X-ray, CT, MRI, etc)

2.5.5 TIA
TIA must be confirmed by a physician, based on central neurological deficits, hemiparesis, hemi- tempo reduction, aphasia, dysarthria, or sensoric deficit from a suspected cerebrovascular origin. Coordination disturbances and balance problems in relation to vertigo (gyratoric or nautic) will be judged by the End point committee in each individual case, and must be seen in relation with other symptoms and signs indicating a brain stem/cerebellum disorder (diplopia, other sight disturbances etc.).
Uncharacteristic dizziness is not sufficient for this diagnosis.

1.3.5/2.5.6 Stroke related to an invasive procedure
Stroke occurring after an invasive procedure, and not later than the day following the procedure.