ORIGINAL ARTICLE

Folate Therapy and In-Stent Restenosis after Coronary Stenting

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ABSTRACT

BACKGROUND

Vitamin therapy to lower homocysteine levels has recently been recommended for the prevention of restenosis after coronary angioplasty. We tested the effect of a combination of folic acid, vitamin B_6, and vitamin B_{12} (referred to as folate therapy) on the risk of angiographic restenosis after coronary-stent placement in a double-blind, multicenter trial.

METHODS

A total of 636 patients who had undergone successful coronary stenting were randomly assigned to receive 1 mg of folic acid, 5 mg of vitamin B_6, and 1 mg of vitamin B_{12} intravenously, followed by daily oral doses of 1.2 mg of folic acid, 48 mg of vitamin B_6, and 60 μg of vitamin B_{12} for six months, or to receive placebo. The angiographic end points (minimal luminal diameter, late loss, and restenosis rate) were assessed at six months by means of quantitative coronary angiography.

RESULTS

At follow-up, the mean (±SD) minimal luminal diameter was significantly smaller in the folate group than in the placebo group (1.59±0.62 mm vs. 1.74±0.64 mm, P=0.008), and the extent of late luminal loss was greater (0.90±0.55 mm vs. 0.76±0.58 mm, P=0.004). The restenosis rate was higher in the folate group than in the placebo group (34.5 percent vs. 26.5 percent, P=0.05), and a higher percentage of patients in the folate group required repeated target-vessel revascularization (15.8 percent vs. 10.6 percent, P=0.05). Folate therapy had adverse effects on the risk of restenosis in all subgroups except for women, patients with diabetes, and patients with markedly elevated homocysteine levels (15 μmol per liter or more) at baseline.

CONCLUSIONS

Contrary to previous findings, the administration of folate, vitamin B_6, and vitamin B_{12} after coronary stenting may increase the risk of in-stent restenosis and the need for target-vessel revascularization.

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Homocysteine is believed to be a risk factor for coronary artery disease.[1,2] Folate supplementation is a cost-effective way to treat hyperhomocysteinemia.[3,4] Studies in animals have shown that homocysteine levels are related to the risk of restenosis after carotid angioplasty,[5,6] because high levels promote thrombogenicity[7,8] and neointimal proliferation.[9] In rats, folate supplementation lowered homocysteine levels and inhibited neointimal hyperplasia after carotid endarterectomy.[10] In humans, data regarding homocysteine levels and the risk of restenosis after coronary angioplasty have been conflicting.[11-18] The recent finding that the rate of restenosis was significantly reduced after coronary angioplasty among patients who received folate in combination with vitamins B_6 and B_{12} (referred to as folate therapy)[19] has led some interventionalists to adopt the use of folate therapy after coronary interventions. However, in that trial, folate treatment seemed to be more effective after balloon angioplasty than after coronary stenting; the latter is now the method of choice for the vast majority of patients undergoing coronary intervention. We therefore evaluated the efficacy of vitamin therapy for the prevention of restenosis in patients undergoing coronary stenting.

METHODS

STUDY DESIGN

This double-blind, placebo-controlled, randomized trial, conducted in Germany and the Netherlands, was approved by the local ethics committees in each country, and written informed consent was obtained from all patients. Between November 1998 and September 2000, 636 patients who had undergone successful coronary stenting were enrolled at two centers (446 in Bremen, Germany, and 190 in Zwolle, the Netherlands). Exclusion criteria were in-stent restenosis, significant left-main-artery stenosis and bifurcation lesions, myocardial infarction less than 24 hours before enrollment, renal dysfunction (defined by a serum creatinine level of more than 1.3 mg per deciliter [115 μmol per liter]), and current intake of vitamins. Patients were assigned to receive folate therapy — an intravenous bolus injection of 1 mg of folic acid, 5 mg of vitamin B_6, and 1 mg of vitamin B_{12}, followed by daily oral administration of 1.2 mg of folic acid, 48 mg of vitamin B_6, and 60 μg of vitamin B_{12} — or placebo. Study medication was provided at no charge by Medice. Plasma levels of homocysteine were measured at baseline and at six months in all patients after an overnight fast. Samples were analyzed by high-performance liquid chromatography. Patients were followed by monthly telephone contact and were questioned about adherence to the study regimen. Eighty patients agreed to return for laboratory follow-up at one month. All patients were asked to return after six months for angiographic follow-up. If clinically indicated, follow-up angiography was performed earlier. Patients who underwent early follow-up angiography (within four months after the initial procedure) were asked to undergo the scheduled follow-up angiography after six months as well, if no restenosis was found. All investigators agreed to perform repeated target-lesion revascularization according to the following prespecified guidelines: if the degree of stenosis was between 75 percent and 90 percent, the lesion was redilated only if clinically significant signs or symptoms of ischemia were present, and if the degree of stenosis exceeded 90 percent, redilation was always encouraged. Adherence to the study medication was confirmed by a pill count at follow-up. The trial was coordinated by Diagram (Zwolle, the Netherlands).

CORONARY-STENT PLACEMENT

Coronary stents were placed according to standard techniques. Only bare-metal stents were used, and the choice of stent was left to the operator. All patients received 300 mg of clopidogrel orally immediately after the procedure, followed by 75 mg daily for four weeks, and 100 mg of aspirin daily. Procedural success was defined as residual stenosis of less than 20 percent in the absence of closure during the first 48 hours after the procedure.[20]

QUANTITATIVE CORONARY ANGIOGRAPHY

Coronary angiograms were obtained at baseline, immediately after stenting, and at follow-up; two identical orthogonal views were obtained after the intracoronary administration of nitrates and stored on digital CD-ROM. End-diastolic frames were chosen for quantitative analysis, which was performed in a blinded fashion by an independent core laboratory (Diagram). The reference diameter, minimal luminal diameter, degree of stenosis, and lesion length were calculated as the average value of the two orthogonal views. The same views and calibration were used at follow-up angiogra-

Table 1. Baseline Characteristics and Laboratory Findings.*

Characteristic	Folate Group (N=316)	Placebo Group (N=320)	P Value
Demographic characteristics			
Age — yr	61.4±9.8	61.3±10.8	0.83
Female sex — no. (%)	76 (24.1)	70 (21.9)	0.51
Clinical characteristics			
Cardiac risk factors — no. (%)			
Diabetes	52 (16.5)	41 (12.8)	0.19
Low-carbohydrate and low-glucose diet	13 (4.1)	9 (2.8)	
Oral hypoglycemic therapy	33 (10.4)	25 (7.8)	
Insulin	6 (1.9)	7 (2.2)	
Smoking	93 (29.4)	107 (33.4)	0.28
Hypercholesterolemia	191 (60.4)	182 (56.9)	0.36
Previous cardiovascular events — no. (%)			
Myocardial infarction	110 (34.8)	119 (37.2)	0.51
Coronary bypass grafting	17 (5.4)	22 (6.9)	0.43
Medical therapy — no. (%)			
Glycoprotein IIb/IIIa inhibitors	35 (11.1)	36 (11.2)	0.94
Statins	119 (37.7)	133 (41.6)	0.31
Beta-blockers	219 (69.3)	228 (71.2)	0.59
Angiotensin-converting–enzyme inhibitors	90 (28.5)	76 (23.8)	0.17
Laboratory findings†			
Homocysteine — μmol/liter			
Baseline	12.2±4.6	12.9±5.1	0.06
1 Mo	8.7±2.5	13.7±7.5	<0.001
Follow-up	9.0±3.2	13.3±4.9	<0.001
Total cholesterol — mg/dl			
Baseline	197.9±48.0	197.2±46.3	0.86
Follow-up	186.1±41.9	186.1±42.8	0.99
HDL cholesterol — mg/dl			
Baseline	42.8±11.8	42.3±12.5	0.63
Follow-up	47.6±13.3	45.4±12.7	0.08
LDL cholesterol — mg/dl			
Baseline	129.8±43.1	129.5±43.0	0.94
Follow-up	116.0±40.3	116.5±38.0	0.94
Triglycerides — mg/dl			
Baseline	139.2±116.2	138.6±118.8	0.95
Follow-up	126.8±79.0	141.2±111.9	0.11

* Plus–minus values are means ±SD.
† To convert values for high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

phy. Restenosis was defined as stenosis of more than 50 percent of the luminal diameter. Late luminal loss was defined as the difference between the minimal luminal diameter immediately after the procedure and that at follow-up. Acute gain was defined as the difference between the minimal luminal diameter before the procedure and that immediately after the procedure. The loss index was calculated as late loss divided by acute gain. The target lesion was defined as the segment covered

Table 2. Angiographic Results for 521 Lesions in 483 Patients with Angiographic Follow-up.*

Variable	Folate Group	Placebo Group	P Value
Location of lesion — no. of lesions (%)			
Left anterior descending coronary artery	127 (48.1)	115 (44.7)	0.44
Proximal left anterior descending coronary artery	48 (18.2)	48 (18.7)	0.88
Circumflex coronary artery	51 (19.3)	51 (19.8)	0.71
Right coronary artery	80 (30.3)	83 (32.3)	0.62
Bypass graft	6 (2.3)	8 (3.1)	0.96
Complex lesion†	214 (81.1)	205 (79.8)	0.52
Lesion length — mm	8.61±4.12	8.28±3.70	0.35
Reference-vessel diameter — mm			
Before stenting	2.86±0.52	2.87±0.52	0.89
After stenting	3.09±0.49	3.08±0.46	0.78
At follow-up	2.89±0.48	2.94±0.52	0.29
Minimal luminal diameter — mm			
Before stenting	0.94±0.36	0.98±0.38	0.23
After stenting	2.50±0.40	2.50±0.41	0.97
At follow-up	1.59±0.62	1.74±0.64	0.008
Changes in minimal luminal diameter — mm			
Acute gain	1.56±0.44	1.52±0.45	0.33
Late loss	0.90±0.55	0.76±0.58	0.004
Net gain	0.66±0.64	0.76±0.65	0.06
Stenosis — %			
Before angioplasty	66.0±11.6	65.7±12.3	0.21
After angioplasty	18.8±7.1	18.7±6.7	0.83
At follow-up	45.1±18.0	41.0±18.1	0.01
Restenosis — no. of lesions (%)‡	91 (34.5)	68 (26.5)	0.05

* Plus–minus values are means ±SD. The patients in the folate group had a total of 264 lesions, and those in the placebo group had a total of 257.
† Complex lesions are defined as B1, B2, or C according to the classification of the American College of Cardiology–American Heart Association.
‡ Restenosis is defined as stenosis of more than 50 percent at follow-up.

by the stent plus the 5-mm segments adjacent to the proximal and distal edges of the stent.

END POINTS

The primary angiographic end point was the minimal luminal diameter within the target lesion at follow-up. Secondary end points were late luminal loss and restenosis. Primary clinical end points were events related to restenosis: death from cardiac causes, target-vessel myocardial infarction (defined by an increase in the creatine kinase level to more than three times the normal value and electrocardiographic changes in the distribution of the target vessel), and target-vessel revascularization (defined as redilation owing to in-segment restenosis or bypass surgery prompted by restenosis).

STATISTICAL ANALYSIS

We estimated that 622 patients would need to be enrolled for the study to have the statistical power to detect a difference in late luminal loss of 0.13 mm between the two groups with 90 percent power, assuming a standard deviation of 0.50 mm in each group, using a two-group t-test and a two-sided significance level of 0.05. To account for the prob-

ability that some patients would not complete the study protocol, we planned to enroll 650 patients.

For continuous variables, differences between the two groups were calculated by analysis of variance or Wilcoxon's rank-sum test. For discrete variables, differences were analyzed with the chi-square test or Fisher's exact test. The Breslow–Day test was used to examine the statistical evidence of heterogeneity among subgroups.

A multiple logistic-regression analysis was performed to identify independent variables associated with restenosis. The stepwise selection of the variable and the estimation of significant probabilities were performed by means of the maximum-likelihood ratio test. The chi-square value was calculated from the log of the ratio of maximum-partial-likelihood functions. The additional value of each category of variables added sequentially was evaluated on the basis of the increases in the overall likelihood statistic ratio. The following variables, if significant on univariate analysis, were included in the multivariate analysis: age; sex; the presence or absence of diabetes (defined by current use of insulin or oral hypoglycemic therapy), smoking, previous myocardial infarction, previous bypass surgery, and use of glycoprotein IIb/IIIa inhibitors; baseline and follow-up levels of homocysteine, cholesterol, and triglycerides; lesion length; reference diameter; postprocedural minimal luminal diameter; and type of therapy at discharge (statins, beta-blockers, and angiotensin-converting–enzyme inhibitors).

Adverse events during follow-up were analyzed by the Kaplan–Meier method. Differences in the event-free survival curves between the two groups were compared with the use of the log-rank test. Data analysis was performed by an independent core laboratory (Diagram). The investigators initiated the study, wrote the article, and had full access to the data.

RESULTS

A total of 636 patients were enrolled: 316 were randomly assigned to receive folate therapy, and 320 to receive placebo. All 636 patients were included in the analysis of clinical end points. During follow-up, 91 patients discontinued treatment: 42 (13.3 percent) in the folate group and 49 (15.3 percent) in the placebo group (P=0.47); in no case was treatment discontinued because of side effects. The remaining 545 patients completed the study.

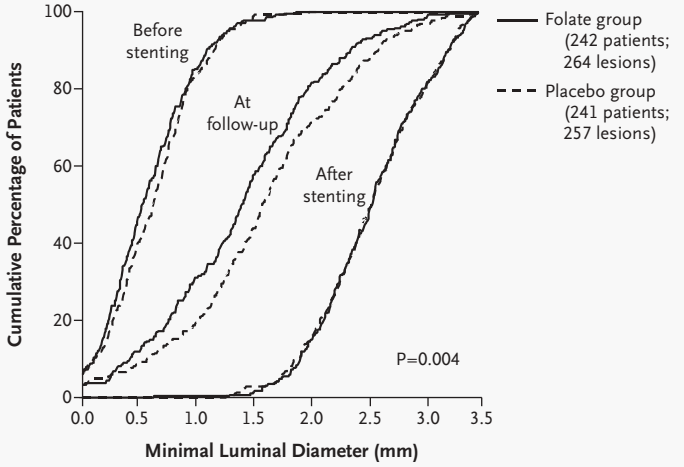

Figure 1. Cumulative Distribution of the Minimal Luminal Diameter before and Immediately after Stent Implantation and at Follow-up Angiography in the Folate Group and the Placebo Group.

A significant shift to the left is seen at follow-up in the folate group, indicating that the minimal luminal diameter was smaller in this group than in the placebo group.

No follow-up angiography was obtained in 62 patients (60 declined, and 2 died), leaving 483 patients (242 [76.6 percent] in the folate group and 241 [75.3 percent] in the placebo group, P=0.71) with angiographic follow-up. The rate of statin use at the six-month follow-up visit was 40.6 percent in the folate group and 45.5 percent in the placebo group (P=0.22).

CLINICAL AND LABORATORY CHARACTERISTICS

Clinical and laboratory data were similar in the groups at baseline (Table 1). Homocysteine levels decreased significantly at both one month (from a mean of 12.2 μmol per liter at baseline to 8.7 μmol per liter, P<0.001) and six months (9.0 μmol per liter, P<0.001) in the folate group, but not in the placebo group.

ANGIOGRAPHIC ANALYSIS

The characteristics of the target lesion were well matched in the two study groups (Table 2). The mean (±SD) duration of angiographic follow-up was 210±20 days.

The primary angiographic end point — minimal luminal diameter — was significantly smaller in the folate group than in the placebo group at follow-up (1.59±0.62 vs. 1.74±0.64 mm, P=0.008). Conversely, the extent of late luminal loss was sig-

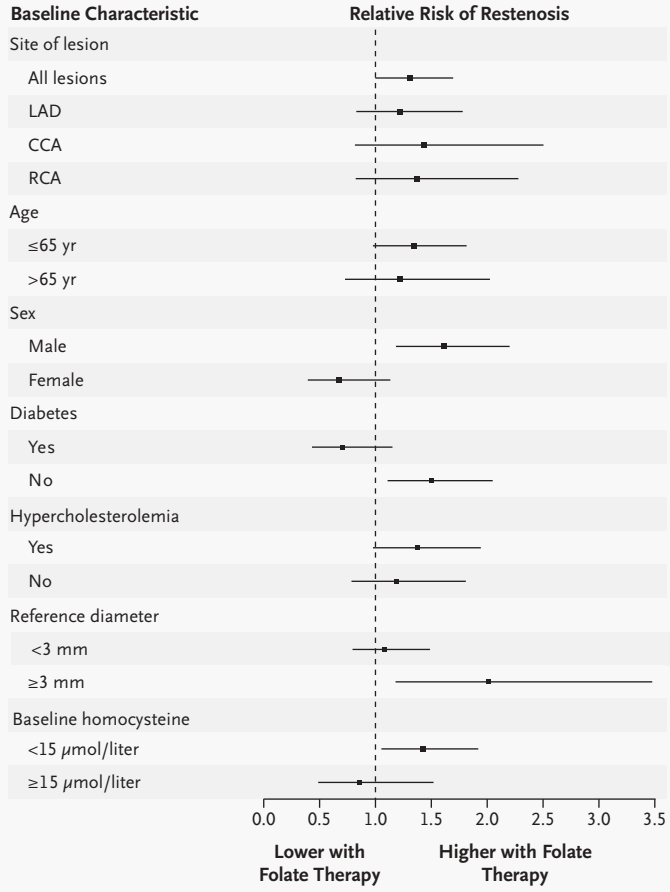

Figure 2. Relative Risk of Restenosis with Folate Therapy, According to Baseline Characteristics.

Squares indicate means, and horizontal lines 95 percent confidence intervals. Folate therapy did not uniformly increase the risk of restenosis. Women (P for heterogeneity=0.002), patients with diabetes (P for heterogeneity=0.02), and patients with high baseline homocysteine levels tended to have a lower risk of restenosis with folate therapy. LAD denotes left anterior descending coronary artery, CCA circumflex coronary artery, and RCA right coronary artery.

nificantly greater in the folate group than in the placebo group (0.90±0.55 vs. 0.76±0.58 mm, P=0.004), as was the loss index (late luminal loss divided by acute gain) (0.61±0.38 vs. 0.51±0.41, P=0.006). The restenosis rate was higher in the folate group than in the placebo group (34.5 percent vs. 26.5 percent; relative risk, 1.30; 95 percent confidence interval, 1.00 to 1.69; P=0.05). The cumulative distribution curves of the minimal luminal diameter are shown in Figure 1. At follow-up, the curve showed a significant leftward shift in the folate group, indicating a higher frequency of smaller luminal diameters (P=0.004).

We performed subgroup analyses of the relative risk of restenosis in order to evaluate whether the increase in restenosis was distributed evenly across subgroups (Fig. 2). The point estimates showed that folate therapy reduced the risk of restenosis, but not significantly so, among women (relative risk, 0.67; 95 percent confidence interval, 0.39 to 1.14; P=0.13; P for heterogeneity=0.002), and among patients with diabetes, as compared with patients without diabetes (relative risk, 0.71; 95 percent confidence interval, 0.44 to 1.15; P=0.16; P for heterogeneity=0.02). Likewise, patients with baseline homocysteine levels of 15 μmol per liter or more had a decreased risk of restenosis with the use of folate therapy (relative risk, 0.86; 95 percent confidence interval, 0.49 to 1.52; P=0.61), whereas those with lower levels of homocysteine had an increase in risk (relative risk, 1.42; 95 percent confidence interval, 1.05 to 1.92; P=0.02; P for heterogeneity=0.12). The adverse effect of folate therapy was most pronounced in patients who had vessels with a reference diameter of 3 mm or more (relative risk, 2.02; 95 percent confidence interval, 1.18 to 3.48; P=0.008).

Variables related to restenosis on univariate analysis were lesion length (P=0.001) and the minimal luminal diameter after the procedure (P=0.003). There were no significant differences between patients with and those without restenosis in homocysteine levels at baseline (P=0.71) or follow-up (P=0.52) or in statin use (42.1 percent vs. 41.7 percent, P=0.93). On multivariate analysis, only the lesion length (P=0.002) and the minimal luminal diameter after the procedure (P=0.001) significantly affected the risk of restenosis.

CLINICAL END POINTS

Table 3 summarizes the clinical end points in the two groups after 165 days of follow-up (before the planned angiographic follow-up) and after 250 days of follow-up (after the 6-month angiographic follow-up). The analysis of target-vessel revascularization at 165 days, which included only clinically driven reinterventions, showed that 24 patients (7.6 percent) in the folate group and 14 patients (4.4 percent) in the placebo group underwent target-vessel revascularization (P=0.09). By 250 days of follow-up, an analysis that included clinically and angiographically driven reinterventions showed that 50 patients (15.8 percent) in the folate group and 34 patients (10.6 percent) in the placebo group had required a second revascularization procedure

(P=0.05). The incidence of death and myocardial infarction did not differ significantly between the two groups at either 165 or 250 days. The use of statin therapy did not affect the rate of target-vessel revascularization (14.5 percent among patients who received statin therapy, as compared with 12.4 percent among those who did not receive statin therapy; P=0.46).

DISCUSSION

We found that therapy with folate, vitamin B_6, and vitamin B_{12} had an adverse effect on the risk of restenosis among patients who had received a coronary stent, even though it profoundly lowered plasma homocysteine levels. Despite the fact that hyperhomocysteinemia has been shown to promote the restenotic process after coronary angioplasty in animals,[7-9,21-23] the extent of the role of homocysteine levels in the risk of restenosis in humans has been a subject of controversy.

In accordance with several previous studies,[16-18] but in contrast to others,[11-15] we did not find that the homocysteine level was a predictor of restenosis. With respect to the effect of folate, Schnyder et al.[19] reported that folate therapy resulted in an impressive reduction in the rate of restenosis (from 37.6 percent in the control group to 19.6 percent in the folate group), as well as in the need for target-lesion revascularization (from 22.3 percent to 10.8 percent). Our trial differed in several respects from that of Schnyder et al. First, only approximately half of their patients received stents, and the benefits of folate therapy were evident predominantly in patients who were treated with balloon angioplasty alone. The proliferation of smooth-muscle cells and matrix formation are the most important mechanisms leading to restenosis after coronary stenting,[24] whereas after balloon angioplasty, thrombus formation within intimal cracks and vascular remodeling are of predominant importance to the process of restenosis; the latter changes are potentially more susceptible to the folate-induced effects of homocysteine lowering. Second, the dose of pyridoxal phosphate (vitamin B_6) that we administered was nearly five times as high as that in the study by Schnyder et al. (48 mg vs. 10 mg). Third, none of their patients had homocysteine levels of more than 13.5 μmol per liter at baseline, and no subgroup analysis was performed according to baseline homocysteine levels.

Folate may play a crucial role in the synthesis of DNA and RNA.[25] The administration of high doses of folate vigorously promotes the growth of neointimal cells by providing large amounts of the biochemical precursors needed for cell replication.[26] Because it converts homocysteine to methionine, folate is essential for the formation of *S*-adenosylmethionine, the universal methyl donor and coenzyme for a large number of cell reactions.[27] The homocysteine precursor *S*-adenosylhomocysteine is a powerful competitive inhibitor of *S*-adenosylmethionine–dependent methyltransferases.[28] Therefore, by decreasing homocysteine levels, folate can favorably influence the ratio of *S*-adenosylmethionine to *S*-adenosylhomocysteine and increase the availability of methyl groups for DNA methylation.[29] Homocysteine is metabolized by two main pathways, the vitamin B_6–dependent transsulfuration pathway and the folate-dependent remethylation pathway. The relatively high dose of vitamin B_6 given in our study (48 mg) may have led the transsulfuration pathway to predominate, thereby further decreasing the inhibition of *S*-adenosylhomocysteine as well as *S*-adenosylmethionine and contributing to increased DNA methylation.

Table 3. Clinical End Points at 165 and 250 Days.*

Clinical End Point	Folate Group (N = 316)	Placebo Group (N = 320)	P Value
	number (percent)		
165 days			
Death	1 (0.3)	1 (0.3)	1.00
Acute myocardial infarction in target vessel	3 (0.9)	1 (0.3)	0.37
CABG	4 (1.3)	4 (1.2)	1.00
Repeated PCI	20 (6.3)	10 (3.1)	0.06
Target-vessel revascularization	24 (7.6)	14 (4.4)	0.09
Major adverse coronary events	27 (8.5)	15 (4.7)	0.06
250 days			
Death	1 (0.3)	1 (0.3)	0.99
Acute myocardial infarction in target vessel	3 (0.9)	2 (0.6)	0.64
CABG	8 (2.5)	5 (1.6)	0.34
Repeated PCI	42 (13.3)	29 (9.1)	0.09
Target-vessel revascularization	50 (15.8)	34 (10.6)	0.05
Major adverse coronary events	53 (16.8)	35 (10.9)	0.03

* CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

Experiments in animals have shown that folate can promote tumor growth.[30] In transgenic mice with a folate deficiency, folate supplementation significantly increased the induction of breast cancer.[31] A recent study demonstrated that folate can inhibit intimal hyperplasia induced by a high-homocysteine diet in a rat model of carotid endarterectomy.[10] However, a folate-rich diet in the absence of hyperhomocysteinemia is associated with increased intimal hyperplasia. In fact, vitamin therapy should be considered a double-edged sword in patients who have received coronary stents, since the beneficial antiproliferative effects of folate, vitamin B_6, and vitamin B_{12} — exerted by virtue of their ability to reduce homocysteine levels — must be weighed against their potential adverse proliferative effects. We found that folate therapy lowered the rates of restenosis among women, patients with diabetes, and those with a markedly elevated plasma level of homocysteine (15 μmol per liter or more). Thus, homocysteine levels may play a greater role in the development of restenosis in women and patients with diabetes than in other subgroups of patients. With respect to patients with hyperhomocysteinemia, it is plausible that, given its mechanism of action, folate therapy inhibits rather than promotes the development of restenosis.

A major limitation of our study is that, although the rate of angiographic follow-up was similar in the two groups, follow-up angiography was performed in only 76 percent of patients, mainly because of the exclusion of patients who discontinued treatment, rather than because of any influence of the patients' symptoms.[32] Restenosis was evaluated by means of quantitative coronary angiography. The use of intravascular ultrasonography would have enhanced the value of our study. Finally, there was a relatively low rate of statin use in our population. However, statins have not been shown to have any effect on the risk of target-vessel revascularization after stent implantation.[33,34]

Our data do not provide any evidence that folate therapy for the primary or secondary prevention of coronary artery disease is potentially harmful, since the folate group did not have an increased incidence of death or infarction. Our data cannot be interpreted to mean that multivitamin supplementation should be discontinued in patients after coronary stenting. The oral dose of folate that we used — 1.2 mg — is three times the recommended daily dose for vitamin supplements. If, however, physicians decide to administer folate therapy to patients with coronary artery disease and moderate hyperhomocysteinemia even before the results of prospective prevention studies are known, they should exercise caution in the use of this therapy for patients who have just received a stent.

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