Effect of Homocysteine-Lowering Therapy With Folic Acid, Vitamin B<sub>12</sub>, and Vitamin B<sub>6</sub> on Clinical Outcome After Percutaneous Coronary Intervention

The Swiss Heart Study: A Randomized Controlled Trial

Guido Schnyder, MD
Marco Roffi, MD
Yvonne Flammer, MD
Riccardo Pin, MD
Otto Martin Hess, MD

Context Plasma homocysteine level has been recognized as an important cardiovascular risk factor that predicts adverse cardiac events in patients with established coronary atherosclerosis and influences restenosis rate after percutaneous coronary intervention.

Objective To evaluate the effect of homocysteine-lowering therapy on clinical outcome after percutaneous coronary intervention.

Design, Setting, and Participants Randomized, double-blind placebo-controlled trial involving 553 patients referred to the University Hospital in Bern, Switzerland, from May 1998 to April 1999 and enrolled after successful angioplasty of at least 1 significant coronary stenosis (≥50%).

Intervention Participants were randomly assigned to receive a combination of folic acid (1 mg/d), vitamin B<sub>12</sub> (cyanocobalamin, 400 µg/d), and vitamin B<sub>6</sub> (pyridoxine hydrochloride, 10 mg/d) (n=272) or placebo (n=281) for 6 months.

Main Outcome Measure Composite end point of major adverse events defined as death, nonfatal myocardial infarction, and need for repeat revascularization, evaluated at 6 months and 1 year.

Results After a mean (SD) follow-up of 11 (3) months, the composite end point was significantly lower at 1 year in patients treated with homocysteine-lowering therapy (15.4% vs 22.8%; relative risk [RR], 0.68; 95% confidence interval [CI], 0.48-0.96; P = .03), primarily due to a reduced rate of target lesion revascularization (9.9% vs 16.0%; RR, 0.62; 95% CI, 0.40-0.97; P = .03). A nonsignificant trend was seen toward fewer deaths (1.5% vs 2.8%; RR, 0.54; 95% CI, 0.16-1.70; P = .27) and nonfatal myocardial infarctions (2.6% vs 4.3%; RR, 0.60; 95% CI, 0.24-1.51; P = .27) with homocysteine-lowering therapy. These findings remained unchanged after adjustment for potential confounders.

Conclusion Homocysteine-lowering therapy with folic acid, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> significantly decreases the incidence of major adverse events after percutaneous coronary intervention.

JAMA. 2002;288:973-979

©2002 American Medical Association. All rights reserved.

(Reprinted) JAMA, August 28, 2002—Vol 288, No. 8 973
Homocysteine-lowering therapy at 6 months.

**METHODS**

The protocol was approved by the Institutional Research Ethics Committee of the University Hospital in Bern, Switzerland. Each patient gave written informed consent. This was a prospective study enrolling 553 consecutive patients from May 1998 to April 1999 who had undergone angioplasty of at least 1 significant coronary stenosis (>50%) (Figure 1). After successful coronary angioplasty, patients were randomly assigned in double-blind fashion to receive folic acid (1 mg/d), vitamin B12 (400 µg/d), and vitamin B6 (10 mg/d) or placebo daily for 6 months. The study medication was formulated to obtain a maximal homocysteine-lowering effect with a minimal risk of adverse effects. The study population included a subgroup of 205 patients independently randomized and scheduled for follow-up angiography at 6 months; the quantitative angiography results of this subgroup have been published. Patients with unstable angina, subacute myocardial infarction (<2 weeks), renal insufficiency (serum creatinine level >1.8 mg/dl [160 µmol/L]), or taking vitamin supplements were not included. Patients were asked to withhold any multivitamin intake for the entire study duration. Fasting total plasma homocysteine levels were measured on admission and at 6 months follow-up using a rapid high-performance liquid chromatographic assay. Coronary angioplasty was performed according to standard clinical practice, with success defined as residual diameter stenosis less than 35% with normal flow pattern (Thrombolysis in Myocardial Ischemia [TIMI] III trial criteria). Coronary angiograms were reviewed by an experienced interventional cardiologist blinded to patients’ homocysteine level and treatment assignments.

**Follow-up and Study End Points**

Clinical follow-up, including noninvasive stress test and resting electrocardiogram, was performed at 6 months and 1 year, or earlier if symptoms recurred. Adverse events were defined prospectively as (1) death; (2) cardiac death, defined as sudden, unexplained death or death related to myocardial infarction; (3) nonfatal myocardial infarction, defined as new Q waves (>40 ms; >0.2 mV) in 2 or more contiguous electrocardiographic leads; (4) need for repeat revascularization for proven ischemia demonstrated by either follow-up cardiac events or a positive noninvasive stress test with significant angiographic stenosis of at least 50%; and (5) a composite of major adverse events defined as any of the above events. Patients with more than 1 event had only the first occurring event computed for overall major adverse events determination.

**Statistical Analysis**

The target sample size of 555 patients was based on the assumption that the rate of major adverse events would be 25% or more in the placebo-treated group and less than 15% in the group treated with folate+B12+B6. Assuming a 10% dropout rate, the planned sample size would yield 500 patients with complete follow-up and give the study a statistical power of 80% at a significance level of .05. All analyses were performed with the intent-to-treat principle, and patients lost to follow-up were censored at the time clinical data became no longer available.
Plasma homocysteine levels were positively skewed and therefore log-transformed prior to analysis. Results are shown in natural units. Categorical variables are reported as counts (percentages) and continuous variables as mean (SD). Categorical variables were examined by χ² test. Continuous variables were examined by a 2-tailed t test or by the Mann-Whitney U test if skewed. The Spearman rank correlation coefficient was used to estimate the correlation between homocysteine levels and different continuous variables.

Kaplan-Meier survival curves were used to evaluate freedom from major adverse events, and treatment effect differences were assessed with the Mantel-Cox log-rank test. Cox proportional hazards regression models were used to examine the relation between treatment groups and the different end points, after adjustment for multiple clinical and angiographic covariates including age, sex, use or nonuse of stent, treatment of restenotic or de novo lesions, vessel size, postprocedural minimal luminal diameter, target lesion location, and use or nonuse of glycoprotein IIb/IIIa inhibitors. Selected variables were those that were associated with at least 1 of the end points in unadjusted analysis. Cardiovascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, smoking status) and statin use were not associated with the different end points in unadjusted analysis. Furthermore, adjustment for those variables did not significantly modify the Cox proportional hazards regression analysis and were thus not included in the model. Patients with a history of renal failure were thus not included in the model. Seventy patients (110 lesions) were lost to follow-up or did not comply with the study protocol: 14 (6 in the folate+B₁₂+B₆ group) discontinued study medication, 37 (15 in the folate+B₁₂+B₆ group) refused noninvasive stress testing, 17 (8 in the folate+B₁₂+B₆ group) with proven ischemia refused reangiography, and 2 (1 in the folate+B₁₂+B₆ group) developed reversible contrast agent nephropathy. Two patients randomized to receive folate+B₁₂+B₆ discontinued study medication because of pruritus. No other adverse effect was reported. The baseline clinical, laboratory, and angiographic characteristics of the 70 patients without complete follow-up did not significantly differ from the remaining study population. Given that clinical outcomes were the primary end points in this study, all analyses were performed with the intent-to-treat principle.

**Baseline Characteristics**

Patients in the 2 groups were well matched at baseline with regard to demographic variables and cardiovascular risk factors (Table 1). Severity of coronary artery disease (as measured by a history of previous myocardial infarction, previous revascularization, and the number of treated lesions per patient), baseline laboratory values, and discharge drug therapy were not sig-

---

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Folate+B₁₂+B₆ (n = 272)</th>
<th>Placebo (n = 281)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>79</td>
<td>82</td>
<td>.42</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63.4 (10.6)</td>
<td>61.8 (11.0)</td>
<td>.10</td>
</tr>
<tr>
<td>Smoker, No. (%)</td>
<td>110 (40)</td>
<td>116 (41)</td>
<td>.87</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>77 (28)</td>
<td>77 (27)</td>
<td>.83</td>
</tr>
<tr>
<td>Arterial hypertension, No. (%)</td>
<td>177 (65)</td>
<td>183 (65)</td>
<td>.86</td>
</tr>
<tr>
<td>Hypercholesterolemia, No. (%)</td>
<td>218 (80)</td>
<td>221 (79)</td>
<td>.66</td>
</tr>
<tr>
<td>Previous MI, No. (%)</td>
<td>136 (50)</td>
<td>155 (55)</td>
<td>.27</td>
</tr>
<tr>
<td>MI within last 6 mo, No. (%)</td>
<td>87 (32)</td>
<td>98 (35)</td>
<td>.35</td>
</tr>
<tr>
<td>Previous PTCA, No. (%)</td>
<td>83 (31)</td>
<td>92 (33)</td>
<td>.67</td>
</tr>
<tr>
<td>Previous CABB, No. (%)</td>
<td>35 (13)</td>
<td>34 (12)</td>
<td>.79</td>
</tr>
<tr>
<td>Laboratory findings, mean (SD)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>6.0 (1.1)</td>
<td>6.0 (1.0)</td>
<td>.58</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.04 (0.20)</td>
<td>1.04 (0.19)</td>
<td>.70</td>
</tr>
<tr>
<td>Baseline homocysteine, mg/L</td>
<td>1.54 (0.64)</td>
<td>1.50 (0.62)</td>
<td>.68</td>
</tr>
<tr>
<td>6-month follow-up</td>
<td>1.01 (0.34)</td>
<td>1.36 (0.57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>214 (43)</td>
<td>212 (46)</td>
<td>.29</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>46 (13)</td>
<td>45 (13)</td>
<td>.37</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>130 (37)</td>
<td>130 (40)</td>
<td>.74</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>181 (113)</td>
<td>178 (113)</td>
<td>.86</td>
</tr>
<tr>
<td>Discharge therapy, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>189 (69)</td>
<td>199 (71)</td>
<td>.71</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>106 (61)</td>
<td>179 (64)</td>
<td>.52</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>100 (37)</td>
<td>102 (36)</td>
<td>.94</td>
</tr>
<tr>
<td>Aspirin</td>
<td>252 (93)</td>
<td>265 (94)</td>
<td>.53</td>
</tr>
<tr>
<td>ADP inhibitors</td>
<td>150 (55)</td>
<td>162 (58)</td>
<td>.45</td>
</tr>
</tbody>
</table>

*MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABB, coronary artery bypass graft; HbA₁c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE, angiotensin-converting enzyme; and ADP, adenosine diphosphate.
†Criteria for variables: (1) smoking: current or discontinued during the last 6 months; (2) diabetes mellitus: HbA₁c level at least 6.2% and current insulin or oral hypoglycemic therapy; (3) hypertension: blood pressure greater than 140/90 mm Hg or current antihypertensive therapy; (4) hypercholesterolemia: cholesterol level at least 200 mg/dL or current lipid-lowering drugs.
‡Conversion factors between conventional and SI units: creatinine: 88.4 × mg/dL = µmol/L; homocysteine: 7.397 × mg/L = µmol/L; cholesterol (total, HDL, LDL): 0.0259 × mg/dL = mmol/L; triglycerides: 0.0113 × mg/dL = mmol/L.

---

©2002 American Medical Association. All rights reserved.

©2002 American Medical Association. All rights reserved.
nificantly different between study groups. As expected, mean homocysteine levels (SD) at 6 months were significantly lower with folate+B12+B6 therapy compared with placebo (1.01 [0.34] mg/L [7.5 (2.5) µmol/L] vs 1.36 [0.57] mg/L [10.1 (4.2) µmol/L], \( P < .001 \)). Mild to moderate elevation of homocysteine levels (>1.62 mg/L [12 µmol/L]) was present in 29% of patients at baseline. None of the patients had severe hyperhomocysteinemia (>13.5 mg/L [100 µmol/L]). Baseline homocysteine levels correlated with age (Spearman \( r = 0.212, P < .001 \)), serum creatinine levels (Spearman \( r = 0.251, P < .001 \)), and high-density lipoprotein (HDL) cholesterol levels (Spearman \( r = -0.128, P = .004 \)).

Lesion location was independent of study group: 40% of all lesions were located in the left anterior descending coronary artery and about 30% each in the circumflex coronary artery and the right coronary artery (Table 2). Lesion severity (lesion complexity, lesion length, vessel size, minimal luminal diameter, and diameter stenosis) before and after coronary angioplasty was comparable between study groups. The use of stents and glycoprotein IIb/IIIa inhibitors was also identical between study groups.

**Table 2. Lesion Characteristics and Treatment Options**

<table>
<thead>
<tr>
<th>Lesion location, No. (%)</th>
<th>Folate+B12+B6 (n = 369)</th>
<th>Placebo (n = 372)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>146 (40)</td>
<td>151 (41)</td>
<td>.78</td>
</tr>
<tr>
<td>Circumflex</td>
<td>98 (27)</td>
<td>110 (30)</td>
<td>.36</td>
</tr>
<tr>
<td>Right coronary</td>
<td>125 (34)</td>
<td>111 (30)</td>
<td>.24</td>
</tr>
<tr>
<td>Restenotic lesions, No. (%)</td>
<td>16 (4.4)</td>
<td>20 (5.5)</td>
<td>.50</td>
</tr>
<tr>
<td>Complex lesions, No. (%)</td>
<td>241 (65)</td>
<td>231 (62)</td>
<td>.41</td>
</tr>
<tr>
<td>No. of treated lesions per patient, mean (SD)</td>
<td>1.35 (0.57)</td>
<td>1.34 (0.58)</td>
<td>.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment options, No. (%)</th>
<th>Folate+B12+B6 (n = 369)</th>
<th>Placebo (n = 372)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stents</td>
<td>199 (54)</td>
<td>197 (53)</td>
<td>.79</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>42 (11)</td>
<td>42 (11)</td>
<td>.97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference vessel diameter, mean (SD), mm</th>
<th>Folate+B12+B6 (n = 369)</th>
<th>Placebo (n = 372)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before angioplasty</td>
<td>2.81 (0.67)</td>
<td>2.75 (0.68)</td>
<td>.21</td>
</tr>
<tr>
<td>After angioplasty</td>
<td>3.06 (0.64)</td>
<td>3.01 (0.81)</td>
<td>.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimal luminal diameter, mean (SD), mm</th>
<th>Folate+B12+B6 (n = 369)</th>
<th>Placebo (n = 372)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before angioplasty</td>
<td>0.94 (0.48)</td>
<td>0.88 (0.45)</td>
<td>.16</td>
</tr>
<tr>
<td>After angioplasty</td>
<td>2.35 (0.61)</td>
<td>2.31 (0.77)</td>
<td>.52</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diameter stenosis, mean (SD), %</th>
<th>Folate+B12+B6 (n = 369)</th>
<th>Placebo (n = 372)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before angioplasty</td>
<td>66.6 (14.7)</td>
<td>68.2 (16.4)</td>
<td>.15</td>
</tr>
<tr>
<td>After angioplasty</td>
<td>23.5 (10.2)</td>
<td>23.4 (10.9)</td>
<td>.89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion length, mean (SD), mm</th>
<th>Folate+B12+B6 (n = 369)</th>
<th>Placebo (n = 372)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 (7.8)</td>
<td>12.2 (6.9)</td>
<td>.29</td>
<td></td>
</tr>
</tbody>
</table>

**Study End Points**

After a mean (SD) follow-up of 11 (3) months, 14.0% of patients treated with folate+B12+B6 underwent repeat revascularization vs 19.9% of control patients (relative risk [RR], 0.70; 95% confidence interval [CI], 0.49-1.01; \( P = .06 \)) (Table 3). This difference was primarily due to the number of patients with repeat target lesion revascularization, as 4.0% of patients in the folate+B12+B6 group and 3.9% in the placebo group had revascularization of a lesion other than a target lesion (RR, 1.03; 95% CI, 0.45-2.34; \( P = .94 \)). Among patients who received folate+B12+B6, 9.9% had repeat target lesion revascularization vs 16.0% in the placebo group, a relative reduction of 38% (RR, 0.62; 95% CI, 0.40-0.97; \( P = .03 \)). The need for target lesion revascularization was also significantly associated with smaller vessel size (SD) (2.91 [0.78] mm vs 3.16 [0.79] mm, \( P = .02 \)), smaller postprocedural minimal luminal diameter (SD) (2.22 [0.53] mm vs 2.45 [0.78] mm, \( P = .03 \)), and the restenotic nature of previously treated lesions (RR, 3.36; 95% CI, 1.67-6.76; \( P = .002 \)). Adjustment for multiple risk factors including age, sex, and variables known to influence the need for target lesion revascularization after coronary angioplasty (use of stents, treatment of restenotic lesions, vessel size, postprocedural minimal luminal diameter, target lesion location, use of IIb/IIIa inhibitors) did not significantly change the association between homocysteine-lowering therapy and the need for repeat target lesion revascularization. In Cox proportional hazards regression analysis and were adjusted for age, sex, use or nonuse of stent, treatment of restenotic or de novo lesions, vessel size, postprocedural minimal luminal diameter, target lesion location, and use or nonuse of glycoprotein IIb/IIIa inhibitors.

**Table 3. Clinical Events at 1 Year Follow-up**

<table>
<thead>
<tr>
<th>Events</th>
<th>Folate+B12+B6 (n = 272)</th>
<th>Placebo (n = 281)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>( P ) Value</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target lesion revascularization</td>
<td>27 (9.9)</td>
<td>45 (16.0)</td>
<td>0.62 (0.40-0.97)</td>
<td>.03</td>
<td>0.61 (0.41-0.95)</td>
<td>.02</td>
</tr>
<tr>
<td>Any revascularization</td>
<td>38 (14.0)</td>
<td>56 (19.9)</td>
<td>0.70 (0.49-1.01)</td>
<td>.06</td>
<td>0.69 (0.51-0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>7 (2.6)</td>
<td>12 (4.3)</td>
<td>0.60 (0.24-1.51)</td>
<td>.27</td>
<td>0.57 (0.27-1.42)</td>
<td>.17</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>3 (1.1)</td>
<td>6 (2.1)</td>
<td>0.52 (0.13-2.04)</td>
<td>.34</td>
<td>0.51 (0.15-2.00)</td>
<td>.23</td>
</tr>
<tr>
<td>Any death</td>
<td>4 (1.5)</td>
<td>8 (2.8)</td>
<td>0.54 (0.16-1.70)</td>
<td>.27</td>
<td>0.52 (0.21-1.56)</td>
<td>.17</td>
</tr>
<tr>
<td>Any event</td>
<td>42 (15.4)</td>
<td>64 (22.8)</td>
<td>0.68 (0.48-0.96)</td>
<td>.03</td>
<td>0.66 (0.47-0.94)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Hazard ratio and \( P \) values were determined by Cox proportional hazards regression analysis and were adjusted for age, sex, use or nonuse of stent, treatment of restenotic or de novo lesions, vessel size, postprocedural minimal luminal diameter, target lesion location, and use or nonuse of glycoprotein IIb/IIIa inhibitors.
hazards regression analysis, only folate+\text{B}_{12}+\text{B}_{6} therapy (P = 0.02), the
restenotic nature of previously treated les-
ions (P = 0.005), and postprocedural minimal luminal diameter (P = 0.01) re-
tained statistical significance.

The need for target lesion revascular-
ization was independent of chole-
sterol levels, but the benefit of folate+\text{B}_{12}+\text{B}_{6} therapy was most apparent for
patients in the highest cholesterol ter-
tile. Compared with controls, patients
in the highest tertile (\textgreater 228 mg/dL
[5.90 mmol/L]) tertile had the largest
risk reduction in terms of target lesion revascularization (RR, 0.44; 95% CI,
0.21-0.92; P = 0.04). This benefit was not
significant among patients treated with
folate+\text{B}_{12}+\text{B}_{6} in the middle (189-228
mg/dL [4.89-5.90 mmol/L]) tertile (RR, 0.55; 95% CI, 0.25-1.23; P = 0.20) and
was smallest in the lowest (<189 mg/dL
[4.89 mmol/L]) tertile (RR, 0.72; 95%
CI, 0.33-1.55; P = 0.53). A similar trend
was seen for low-density lipoprotein
(LDL) cholesterol levels ([highest ter-
tile: >145 mg/dL (3.75 mmol/L); RR,
0.50; 95% CI, 0.26-0.91; P = 0.03]
[middle tertile: 108-145 mg/dL (2.80-
3.75 mmol/L); RR, 0.58; 95% CI, 0.32-
1.14; P = 0.29] [lowest tertile: <108
mg/dL (2.80 mmol/L); RR, 0.66; 95%
CI, 0.25-1.74; P = 0.39], respectively).
Adjustment for statin use did not sig-
nificantly change those associations.

There was a nonsignificant trend for a
lower incidence of nonfatal myocardial
infarction (RR, 0.60; 95% CI, 0.24-
1.51; P = 0.27), cardiac deaths (RR, 0.52;
95% CI, 0.13-2.04; P = 0.34), and over-
al deaths (RR, 0.54; 95% CI, 0.16-
1.70; P = 0.27) in patients receiving
folate+\text{B}_{12}+\text{B}_{6} therapy. Older age (SD)
was the only variable significantly as-
associated with mortality (65.4 [11.5]
years vs 61.2 [10.8] years, P = 0.002).

The incidence of major adverse
drugs. These results are consistent with
those of recent randomized trials with
folate+\text{B}_{12}+\text{B}_{6} therapy. The outcome
after coronary angioplasty remained un-
altered after adjustment for those risk
factors. These results are consistent with
those of recent randomized trials with
homocysteine-lowering therapy show-
ing decreased risk of atherosclerotic
coronary events among healthy pa-
tients.\textsuperscript{27} halting in the progress-
ion of carotid plaque,\textsuperscript{28} improved arteri-
olar endothelial function,\textsuperscript{29,31} and signif-
icant benefit on restenosis rate after coro-
nary angioplasty.\textsuperscript{19}

This study further suggests that the
benefit obtained with homocysteine-
lowering therapy at 6 months is main-
tained at 1 year despite cessation of
folate+\text{B}_{12}+\text{B}_{6} therapy at 6 months. Our
previously reported significant de-
crease in restenosis rate after coronary
angioplasty\textsuperscript{19} could have been ques-
tioned as a temporary benefit triggered
by a homocysteine-lowering therapy-
related delay of the restenosis process.
The current study confirms that a 6-month course of this inexpensive treatment has minimal adverse effects and helps to control excessive restenosis mechanisms. Nevertheless, it is unclear whether a longer treatment course (ie, up to 12 months) would have benefited the other end points, such as death or myocardial infarction, for which only a trend in favor of homocysteine-lowering therapy was found. These issues should be answered by several ongoing clinical trials: the Norwegian Vitamin Interventional Trial (NORVIT) and the Western Norway B-vitamin Intervention Trial (WENBIT) will assess the effects of homocysteine-lowering therapy in patients with coronary artery disease; the Vitamin Intervention for Stroke Prevention (VISP) study in the United States will report the effect of B vitamins on stroke recurrence in patients with cardiovascular disease; and the Prevention with a Combined Inhibitor and Folate in Coronary Heart Disease (PACIFIC) study in Australia and the Study of Effectiveness of Additional Reduction in Cholesterol and Homocysteine (SEARCH) in the United Kingdom will address similar issues.32

The mechanisms by which elevated homocysteine levels impair vascular function and possibly influence outcome after percutaneous coronary intervention are not clearly understood, although several hypotheses have been suggested. Elevated homocysteine levels stimulate vascular smooth muscle cell growth33 and collagen synthesis,33 which promote intimal-medial thickening.34 Elevated homocysteine levels may also have a procoagulant effect through interaction with coagulation factor V,13 protein C,14 tissue plasminogen activator,15 and tissue factor activity.16 However, increasing evidence suggests that the primary mechanism may be oxidative-endothelial injury and dysfunction.31,11 Elevated homocysteine levels decrease the release of nitric oxide35,36 and promote the generation and accumulation of hydrogen peroxide, thus rendering nitric oxide more susceptible to oxidative inactivation.34 Furthermore, elevated plasma homocysteine levels promote lipid peroxidation,37 which alters growth factor production and influences smooth muscle cell proliferation.38 Oxidized LDL cholesterol has been shown to increase smooth muscle cells proliferation and chemotraction,39,40 and enhance platelet-derived growth factor gene expression and receptor formation in vascular smooth muscle cells.11 Therefore, homocysteine-induced endothelial dysfunction and lipid peroxidation may promote smooth muscle cell proliferation, extracellular matrix formation, and ultimately increase the need for repeat target lesion revascularization. Our findings that the benefit of homocysteine-lowering therapy increases with higher levels of LDL cholesterol supports this possible mechanism.

A critical question is whether the benefit of homocysteine-lowering therapy on the outcome after coronary intervention reflects causality. In the current study, the treatment of restenotic lesions, the treatment of lesions in smaller vessels, and smaller postprocedural minimal luminal diameter were all significantly associated with a worse outcome after coronary angioplasty. Adjustment for these factors did not weaken the benefit of homocysteine-lowering therapy, suggesting an independent association.

A limitation of the study design was that it precluded assessment of the separate effects of folic acid, vitamin B12, and vitamin B6, and the effect of different doses of these vitamins. Furthermore, we cannot exclude the possibility that the benefit seen was not also influenced by other homocysteine-independent treatment effects. Specifically, folic acid likely improves nitric oxide availability independently of its homocysteine-lowering effect,41 and vitamin B6 deficiency appears to be an independent predictor of coronary artery disease43 and further has been shown to alter platelet function.42 Therefore, and despite the findings of the Homocysteine Lowering Trialists’ Collaboration group that vitamin B6 does not significantly lower homocysteine levels,40 the inclusion of vitamin B6 in the homocysteine-lowering therapy or possibly another homocysteine-unrelated effect of folic acid or vitamin B12 could have contributed to the improvement seen in the patients treated with folate+B12+B6. In conclusion, the findings in this study, in conjunction with our previously described association between homocysteine levels and restenosis rate,17 support the conclusion that the combination of folic acid, vitamin B12, and vitamin B6, at least partially by lowering of homocysteine levels, is an effective therapy for improving outcome in patients undergoing coronary angioplasty.

Author Contributions: Study concept and design: Schnyder, Hess. Acquisition of data: Schnyder, Roffi, Flammer, Pin. Analysis and interpretation of data: Schnyder, Roffi, Flammer, Pin, Hess. Drafting of the manuscript: Schnyder. Critical revision of the manuscript for important intellectual content: Roffi, Flammer, Pin, Hess. Statistical expertise: Schnyder, Hess. Obtained funding: Schnyder. Administrative, technical, or material support: Schnyder, Roffi, Flammer, Pin. Study supervision: Hess.

Funding/Support: Dr Schnyder is supported by a career development grant from the Swiss National Science Foundation and by the University Hospital, Bern, Switzerland.

Acknowledgment: We would like to thank the patients and their physicians for participation in this study. We are grateful for the cooperation of the Coronary Catheterization Laboratory staff and the nursing staff of the Swiss Cardiovascular Center in Bern.

REFERENCES
9. Tang L, Mamotte CD, Van Bockxmeer FM, Taylor...
HOMOCYSTEINE-LOWERING THERAPY


©2002 American Medical Association. All rights reserved.

(Reprinted) JAMA, August 28, 2002—Vol 288, No. 8 979

Downloaded From: https://jama.jamanetwork.com/ by a Non-Human Traffic (NHT) User on 08/19/2019