Homocysteine Status and Polymorphisms of Methylenetetrahydrofolate Reductase Are Not Associated With Restenosis After Stenting in Coronary Arteries

Werner Koch, Gjin Ndrepepa, Julinda Mehilli, Siegmund Braun, Marc Burghartz, Harald Lengnick, Klaus Kölling, Albert Schömig, Adnan Kastrati

Objective—We investigated the influence of elevated homocysteine plasma levels and 2 polymorphisms, 677C/T and 1298A/C, of the methylenetetrahydrofolate reductase (MTHFR) gene on the risk of restenosis after stenting in patients with symptomatic coronary artery disease.

Methods and Results—Homocysteine levels and MTHFR genotypes were determined in 800 consecutive patients treated with coronary artery stenting. Angiographic restenosis (≥50% diameter stenosis at 6-month follow-up) was present in 25.8% of the patients with low homocysteine levels (at or below the median of 11.6 μmol/L; n=400) and 24.1% of the patients with high homocysteine levels (>11.6 μmol/L; n=400; P=0.62). Rates of angiographic restenosis were 26.0%, 23.5%, and 26.9% in carriers of the 677CC, 677CT, and 677TT genotypes (P=0.75), respectively, and 24.4%, 25.9%, and 24.0% in patients with the 1298AA, 1298AC, and 1298CC genotypes (P=0.90), respectively. The need for restenosis-driven reintervention (clinical restenosis) was 18.8% in subjects with low homocysteine concentrations and 19.0% in subjects with high homocysteine concentrations during the first year after the intervention (P=0.93). Rates of clinical restenosis were 19.5%, 17.1%, and 23.3% in carriers of the 677CC, 677CT, and 677TT genotypes (P=0.37), respectively, and 17.6%, 18.6%, and 24.7% in patients with the 1298AA, 1298AC, and 1298CC genotypes (P=0.27), respectively.

Conclusions—Elevated levels of homocysteine and 2 polymorphisms of the MTHFR gene are not associated with restenosis after stenting in coronary arteries. (Arterioscler Thromb Vasc Biol. 2003;23:2229-2234.)

Key Words: homocysteine ■ methylenetetrahydrofolate reductase ■ stent ■ restenosis ■ genetics

The deployment of endovascular stents offers a significant advance in the percutaneous treatment of atherosclerotic disease, but in-stent restenosis affects ≈30% of patients in the months after an initially successful intervention.1 Elevated homocysteine plasma levels have been associated with the risk of coronary artery disease (CAD), myocardial infarction (MI), and adverse outcome after coronary balloon angioplasty.2–6 Homocysteine levels are determined by environmental and genetic factors, including the single-nucleotide polymorphism (SNP) 677C/T of the gene encoding methylenetetrahydrofolate reductase (MTHFR).7,8 MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is required as a methyl donor for conversion of homocysteine to methionine by methionine synthase.9 The 677C/T SNP affects amino acid 222 (alanine for conversion of homocysteine to methionine by methionine synthase, which may be interpreted as increased risk. For this reason,
determination of patients’ MTHFR genotypes may provide valuable additional information about homocysteine status. In a relatively large number of patients, we investigated the influence of elevated homocysteine levels and polymorphisms (677C/T and 1298A/C) of the MTHFR gene on the rate of restenosis after placement of stents in atherosclerotic coronary arteries.

Methods

Patients
The study included 800 white patients with symptomatic CAD who underwent stent implantation in coronary arteries at Deutsches Herzzentrum München from September 2000 to September 2001. The protocols of stent placement and poststenting therapy have been described in detail elsewhere. Postprocedural pharmacological therapy consisted of aspirin (100 mg twice daily, indefinitely) and clopidogrel (75 mg/d for at least 4 weeks). Patients who were considered at a higher risk for ischemic complications received additional therapy with the glycoprotein IIb/IIIa blocker abciximab, which was given as a bolus injection during the stent insertion procedure and as a 12-hour continuous infusion thereafter. All patients were scheduled for angiographic follow-up at 6 months. Written informed consent was obtained for the intervention itself, routine follow-up angiography at 6 months, and genotype determination. The study protocol conformed to the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

Coronary Angiography
Lesion morphology was classified according to the modified American College of Cardiology/American Heart Association grading system as type A, B1, B2, or C, and lesions of types B2 and C were considered complex lesions. Angiograms were recorded just before the stenting procedure and as a 12-hour continuous infusion thereafter. All patients were scheduled for angiographic follow-up at 6 months. Written informed consent was obtained for the intervention itself.

Quantitative analysis of angiograms (CMS system; Medis Medical Imaging Systems) was performed by operators not involved in the procedure and who were unaware of the laboratory or genetic data.

Measurement of Homocysteine, Folate, and Vitamin B12 Concentrations
Blood samples were taken from individuals in the supine position before cardiac catheterization, collected into heparinized tubes, and immediately after the intervention and at 6-month follow-up. Vitamin B12 concentrations on clinical and angiographic outcomes, patients were divided into 2 groups with the median value of total serum homocysteine levels used as a cutoff point. The 400 patients with homocysteine levels ≤11.6 μmol/L constituted the group with a low homocysteine status, and the 400 patients with homocysteine levels >11.6 μmol/L constituted the group with a high homocysteine status. To examine the impact of the MTHFR gene polymorphisms on outcome measures, patients were analyzed according to genotypes of the 677C/T SNP and the 1298A/C SNP, independent of their homocysteine status.

The primary end point of the study was restenosis. Two definitions of restenosis were used: the incidence of a diameter stenosis of ≥50% at 6-month follow-up angiography (angiographic restenosis) and the need for target-vessel revascularization (TVR; percutaneous transluminal coronary balloon angioplasty or aortocoronary bypass grafting) because of symptoms or signs of ischemia in the presence of angiographic restenosis at the stented site during the first year after stent placement (clinical restenosis). Secondary end points of the study were the incidence of all-cause death and the rate of death or nonfatal MI at 1 year after stenting. The incidence of thrombotic events during the early 30-day period after stenting, resulting in death, acute MI, or urgent TVR, was assessed separately. The diagnosis of acute MI was based on the presence of a clinical episode of prolonged chest pain with either the appearance of 1 or more new pathological Q waves on the ECG or an increase in creatine kinase (or its MB isoenzyme) levels to at least twice the normal upper limit. Creatine kinase levels were determined systematically over 48 hours after the stenting procedure. The follow-up protocol included a phone contact or a medical visit at the outpatient clinic at 30 days and between 9 and 15 months after stent placement and a control angiography at 6 months. Clinical events were assessed on the basis of the information provided by hospital readmission records, the referring physician, or phone interview with the patient. For all patients who reported cardiac symptoms during the phone interview, at least 1 clinical and electrocardiographic evaluation was performed at the outpatient clinic or by the referring physician.

Statistical Analysis
Discrete variables are expressed as counts and percentages and were compared with χ2 test or Fisher exact test, as appropriate. Continuous variables are expressed as mean±SD and were compared by means of the unpaired, 2-sided t test or ANOVA for more than 2 groups. The independent role of homocysteine levels and the polymorphisms was evaluated in a multivariate model (multiple logistic regressions) for restenosis that included the baseline clinical, lesion-related, and procedural characteristics between the 400 patients with low (<11.6 μmol/L) total plasma homocysteine levels. Survival free of MI was analyzed by a Cox regression model that allowed the calculation of hazard ratios and 95% CIs. Statistical analyses were performed with S-Plus software (Mathsoft Inc). A probability value of <0.05 was considered statistically significant.

Results

Patient Characteristics
Table 1 shows a comparison of the baseline clinical, lesion-related, and procedural characteristics between the 400 patients with low (≤11.6 μmol/L) and the 400 patients with high (>11.6 μmol/L) total plasma homocysteine levels. Among the 800 patients, genotypes of the 677C/T SNP were distributed as 43.5% 677CC, 45.3% 677CT, and 11.3% 677TT, and genotypes of the 1298A/C SNP were distributed as 46.1% 1298AA, 41.8% 1298AC, and 12.1% 1298CC. As shown in Table 2, total homocysteine levels were significantly higher among carriers of the 677TT genotype than...
among patients with the 677CC or 677CT genotype (P<0.001). Inversely, significantly higher folate levels were associated with the 677CC genotype than with the 677CT or 677TT genotype (P=0.003; Table 2). Regarding the 1298A/C SNP, homocysteine and folate concentrations were not significantly different between genotypes. Carriers of the genotype combination 677CC/1298AA (CC/AA), CC/AC, CC/CC, CT/AA, CT/AC, or TT/AA were present among the study patients, but not subjects with the genotype combination CT/CC, TT/AC, or TT/CC.

Early Clinical Events
We assessed the occurrence of major adverse clinical events due to thrombosis during the early 30-day period after stenting. Comparison of patients with low homocysteine status and those with high homocysteine status did not indicate significant differences in the incidences of death, death or MI, or urgent TVR (P=0.43). Similarly, these events did not occur at significantly different frequencies among the genotype groups of the 677C/T SNP (P≥0.29) or the 1298A/C SNP (P=0.07).
Six-month angiography of coronary arteries was performed in 306 (76.5%) of patients with low homocysteine status and 295 (73.8%) of patients with high homocysteine status (P = 0.37). The proportion of patients with angiographic restenosis was 25.8% in patients with low homocysteine levels and 24.1% in patients with high homocysteine levels (P = 0.62).

Among patients with angiographic restenosis (n = 150), the mean homocysteine level was 12.1 ± 3.7 μmol/L, and among subjects without angiographic restenosis (n = 451), the mean homocysteine level was 12.7 ± 4.9 μmol/L (P = 0.19). Folate concentration was 9.5 ± 3.3 ng/mL in patients with angiographic restenosis and 9.4 ± 3.1 ng/mL in those without angiographic restenosis (P = 0.76). In addition, the relationship between homocysteine concentrations and angiographic restenosis was determined in quintiles of homocysteine. Within the quintiles, homocysteine concentrations were 3.6 to 9.1 μmol/L, 9.1 to 10.8 μmol/L, 10.8 to 12.5 μmol/L, 12.5 to 15.0 μmol/L, and > 15.0 to 49.1 μmol/L, and the restenosis rates in these groups were 28.8%, 20.5%, 25.0%, 24.8%, and 25.8%, respectively (P = 0.68). Finally, in the uppermost decile (patients with homocysteine concentrations above the 90th percentile of 18.0 μmol/L), the angiographic

### TABLE 2. Characteristics of Patients According to Genotypes of the MTHFR Gene 677C/T Polymorphism (n = 800)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>677CC (n = 348)</th>
<th>677CT (n = 362)</th>
<th>677TT (n = 90)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>64.7 (±10.8)</td>
<td>66.2 (±10.6)</td>
<td>67.1 (±10.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Women</td>
<td>88 (25.3)</td>
<td>96 (26.5)</td>
<td>21 (23.3)</td>
<td>0.81</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>277 (79.6)</td>
<td>286 (79.0)</td>
<td>73 (81.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>241 (69.3)</td>
<td>271 (74.9)</td>
<td>66 (73.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Current smoker</td>
<td>77 (22.1)</td>
<td>72 (19.9)</td>
<td>25 (27.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>84 (24.1)</td>
<td>73 (20.2)</td>
<td>19 (21.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>70 (20.1)</td>
<td>72 (19.9)</td>
<td>17 (18.9)</td>
<td>0.97</td>
</tr>
<tr>
<td>Acute MI</td>
<td>45 (12.9)</td>
<td>60 (16.6)</td>
<td>9 (10.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous MI</td>
<td>111 (31.9)</td>
<td>135 (37.3)</td>
<td>26 (28.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous aortocoronary bypass surgery</td>
<td>46 (13.2)</td>
<td>38 (10.5)</td>
<td>15 (16.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>No. of narrowed coronary arteries</td>
<td></td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>1</td>
<td>84 (24.1)</td>
<td>93 (25.7)</td>
<td>26 (28.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>103 (29.6)</td>
<td>117 (32.3)</td>
<td>27 (30.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>161 (46.3)</td>
<td>152 (42.0)</td>
<td>37 (41.1)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>54.3 (±14.9)</td>
<td>55.5 (±13.7)</td>
<td>52.4 (±12.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>12.0 (±3.9)</td>
<td>12.5 (±4.5)</td>
<td>14.4 (±6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Folate, ng/mL</td>
<td>10.0 (±3.1)</td>
<td>9.3 (±3.1)</td>
<td>9.0 (±3.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Vitamin B12, pg/mL</td>
<td>405 (±269)</td>
<td>392 (±252)</td>
<td>451 (±341)</td>
<td>0.18</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.13 (±0.23)</td>
<td>1.16 (±0.36)</td>
<td>1.12 (±0.25)</td>
<td>0.31</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/dL</td>
<td>39.7 (±46.2)</td>
<td>41.8 (±44.6)</td>
<td>44.2 (±48.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Target coronary vessel</td>
<td></td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>LMCA</td>
<td>9 (2.6)</td>
<td>5 (1.4)</td>
<td>1 (1.1)</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>140 (40.2)</td>
<td>151 (41.7)</td>
<td>41 (45.6)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>72 (20.7)</td>
<td>83 (22.9)</td>
<td>14 (15.6)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>113 (32.5)</td>
<td>113 (31.2)</td>
<td>27 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Venous bypass graft</td>
<td>14 (4.0)</td>
<td>10 (2.8)</td>
<td>7 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Chronic occlusion</td>
<td>16 (4.6)</td>
<td>21 (5.8)</td>
<td>3 (3.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Restenotic lesion</td>
<td>31 (8.9)</td>
<td>31 (8.6)</td>
<td>5 (5.6)</td>
<td>0.58</td>
</tr>
<tr>
<td>Complex lesions (ACC/AHA type B2 or C)</td>
<td>252 (72.4)</td>
<td>282 (77.9)</td>
<td>73 (81.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>12.4 (±7.1)</td>
<td>12.4 (±6.6)</td>
<td>11.9 (±6.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>2.94 (±0.58)</td>
<td>2.95 (±0.59)</td>
<td>2.96 (±0.58)</td>
<td>0.94</td>
</tr>
<tr>
<td>Diameter stenosis before stenting, %</td>
<td>61.7 (±18.8)</td>
<td>62.1 (±18.9)</td>
<td>59.7 (±18.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Stented segment length, mm</td>
<td>21.7 (±10.4)</td>
<td>22.1 (±9.9)</td>
<td>22.6 (±12.9)</td>
<td>0.78</td>
</tr>
<tr>
<td>Percutaneous therapy with abciximab</td>
<td>197 (56.6)</td>
<td>206 (56.9)</td>
<td>50 (55.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>Diameter stenosis after stenting, %</td>
<td>5.1 (±11.8)</td>
<td>4.7 (±9.9)</td>
<td>4.7 (±9.2)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Data are presented as mean (±SD) or number (%) of subjects.
restenosis rate was 19.0%, and the clinical restenosis rate was 17.5%.

Follow-up angiography was done in 262 (75.3%) of the patients with the 677CC genotype, 272 (75.1%) of the patients with the 677CT genotype, and 67 (74.4%) of the patients with the 677TT genotype (P=1). The angiographic restenosis rates were 26.0%, 23.5%, and 26.9% in carriers of the 677CC, 677CT, and 677TT genotype, respectively (P=0.75). Among patients with genotype 1298AA, 1298AC, and 1298CC, follow-up angiography was performed in 275 (74.5%), 251 (75.1%), and 75 (77.3%) subjects, respectively (P=0.98).

The observed angiographic restenosis rates were 24.4%, 25.9%, and 24.0% in carriers of the 1298AA, 1298AC, and 1298CC genotype, respectively (P=0.90). A comparison of the group of patients without angiographic restenosis (n=451) with the group of patients with angiographic restenosis (n=150) showed that the proportion of each MTHFR genotype or genotype combination was not significantly different between the 2 groups (P=0.37).

The independent role of homocysteine level and both polymorphisms was evaluated in a multivariate model of restenosis that included all baseline, lesion-related, and procedural characteristics displayed in Table 1 or Table 2. This model did not show any significant independent association for homocysteine (P=0.15), the 677C/T SNP (P=0.98), or the 1298A/C SNP (P=0.98). In addition, no significant interaction was observed between elevated homocysteine levels and low folate levels with respect to the risk of restenosis (probability value for interaction=0.93).

Clinical Restenosis
The need for restenosis-driven reintervention was 18.8% in the patient group with low homocysteine concentrations and 19.0% in the patient group with high homocysteine concentrations during the first year after stent placement (P=0.93). Patients with genotypes 677CC, 677CT, and 677TT had clinical restenosis rates of 19.5%, 17.1%, and 23.3% (P=0.37), respectively, and patients with genotypes 1298AA, 1298AC, and 1298CC had clinical restenosis rates of 17.6%, 18.6%, and 24.7% (P=0.27), respectively.

One-Year Clinical Outcome
The combined incidence of death and nonfatal MI was 2.5% in the group of patients with low homocysteine status and 4.5% in the group of patients with high homocysteine status (P=0.14, Cox model). Thus, a high homocysteine concentration was associated with a hazard ratio of 1.80 (95% CI 0.83 to 3.91) for the occurrence of death or MI. In the groups with the 677CC, 677CT, and 677TT genotypes, death or nonfatal MI occurred in 3.2%, 3.0%, and 6.7% of the patients, respectively (P=0.24, Cox model). The 677TT genotype was associated with a hazard ratio of 2.14 (95% CI 0.79 to 5.78) when compared with the 677CC genotype. Among patients with the 1298AA, 1298AC, and 1298CC genotypes, the rates of death or nonfatal MI were 3.5%, 3.9%, and 2.1%, respectively (P=0.71, Cox model). The 1298CC genotype was associated with a hazard ratio of 0.59 (95% CI 0.13 to 2.59) compared with the 1298AA genotype. Mortality rates were also not significantly associated with homocysteine levels or MTHFR genotypes.

Discussion
The results presented here strongly suggest that elevated plasma homocysteine concentrations are not associated with an increased risk of restenosis in patients treated with stenting in coronary arteries. In addition, the results provide evidence that the 677C/T SNP and the 1298A/C SNP of the MTHFR gene, either alone or in combination, are not related to in-stent restenosis.

Homocysteine Levels and Restenosis After Coronary Interventions
Experimental studies and clinical trials suggested a possible relationship between high homocysteine levels and restenosis after interventions in coronary arteries.1–6 Elevated plasma homocysteine level was repeatedly reported to be a strong predictor of restenosis and major adverse clinical events after coronary balloon angioplasty.2,6 In contrast to these results obtained in patients with balloon angioplasty, the present data do not suggest the existence of a relationship between homocysteine concentration and the risk of angiographic restenosis or the need for restenosis-driven reintervention after stenting in coronary arteries. In addition, the present results show that levels of total homocysteine were similar in patients with angiographic restenosis and those without angiographic restenosis. The latter finding is in line with a recent result obtained with stenting in Austrian patients and reports on patients from Canada and Israel treated with either stenting or balloon angioplasty.23–25

Relationship Between MTHFR Gene Polymorphisms and Levels of Homocysteine and Folate
In agreement with a number of reports,7,11,12 we found that carriers of the 677TT genotype had significantly higher plasma homocysteine levels than carriers of the 677CC or 677CT genotype. Most likely, the association between the 677TT genotype and elevated homocysteine levels depends on the presence of a low plasma folate status.11,12 Consistent with a previous report on patients with symptomatic atherosclerotic cerebrovascular or peripheral vascular disease,23 the 677CC and 677TT genotype groups among the present study patients exhibited significant differences in plasma folate concentrations. With regard to the 1298A/C SNP, we observed no association with homocysteine or folate levels, which is in agreement with previous publications.14,17

MTHFR Polymorphisms and Restenosis After Stenting
A possible association between the 677C/T SNP and restenosis after stenting was suggested by the findings that the 677T allele or 677TT genotype was related to elevated homocysteine levels7,11,12 and that increased homocysteine levels were associated with the stimulation of inflammatory
reactions and vascular smooth muscle cell proliferation. However, although a relationship between the 677TT genotype and higher plasma homocysteine concentrations was evident in patients in the present study, a linkage between the 677C/T SNP and restenosis was not detected. In a series of 197 Australian subjects, the 677C/T SNP was not significantly related to the occurrence of angiographically documented restenosis after coronary balloon angioplasty. Although this finding is in line with the present data on restenosis after stenting, the present results must not be interpreted merely as a confirmation, because fundamental differences underlie the mechanisms that lead to restenosis after balloon angioplasty and stenting. To the best of our knowledge, the impact of the 1298A/C SNP on restenosis after coronary balloon angioplasty or stenting has not been examined previously.

Study Limitations
Although this is the largest study on the association between homocysteine concentration or MTHFR polymorphisms and restenosis after coronary stenting, it may not be sufficiently powered to detect subtle differences in restenosis. At a 2-sided α-level of 0.05, the study has power values of 83%, 68%, 44%, and 22% to detect increases in the restenosis rate of 40%, 33%, 25%, and 20%, respectively, in the presence of a high homocysteine concentration or carriage of the 677T allele.

Conclusions
Elevated levels of total plasma homocysteine and 2 polymorphisms, 677C/T and 1298A/C, of the MTHFR gene were not associated with restenosis or the occurrence of other major adverse events in a series of 800 patients who underwent stenting in coronary arteries.

References
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