Insertion/Deletion Polymorphism of the Angiotensin I-Converting Enzyme Gene Is Not Associated With Restenosis After Coronary Stent Placement

Werner Koch, PhD; Adnan Kastrati, MD; Julinda Mehilli, MD; Corinna Böttiger, MD; Nicolas von Beckerath, MD; Albert Schömig, MD

**Background**—The renin-angiotensin system is thought to play a role in coronary thrombosis and restenosis. Plasma angiotensin I-converting enzyme (ACE) activity is associated with an insertion/deletion polymorphism in the gene coding for ACE. The objective of this study was to test the hypothesis that the D allele of the ACE gene is associated with a higher risk for restenosis after coronary stent placement.

**Methods and Results**—This prospective study included 1850 consecutive patients with coronary artery disease who underwent intracoronary stent implantation. The adverse clinical events recorded were death, myocardial infarction, and target vessel revascularization. The primary end point of the study was restenosis (≥50% diameter stenosis at follow-up angiography performed in 84% of the patients). The secondary end point was clinical outcome 1 year after the procedure. The restenosis rate at the 6-month angiographic follow-up was 32.8% in patients with the II genotype, 34.0% for patients with the ID genotype, and 31.2% for patients with the DD genotype (P=0.62). One-year event-free survival was 77.7% in patients with genotype II, 75.2% in patients with genotype ID, and 75.5% in patients with genotype DD (P=0.54). The lack of association was also present in the subgroup of patients with a low risk for restenosis: the restenosis rate was 21.7% in II carriers, 23.4% in ID carriers, and 19.7% in DD carriers (P=0.83).

**Conclusions**—The ACE DD genotype or D allele does not influence the 1-year clinical and angiographic outcome of patients undergoing coronary stent placement. These data suggest that routine determination of the ACE genotype may not help identify patients who are at a higher risk of thrombotic and restenotic events after coronary stent placement. (*Circulation*. 2000;102:197-202.)

**Key Words:** genes ■ stents ■ angiotensin ■ restenosis ■ thrombosis

The angiotensin I-converting enzyme (ACE) is a key factor in the production of angiotensin II and in the degradation of bradykinin; these are important peptides involved in cardiovascular physiology. Familial studies have found that the level of plasma ACE is partly under genetic control. Subsequently, it was shown that the D allele of an insertion/deletion (I/D) polymorphism of the gene encoding ACE is associated with higher plasma ACE concentrations. The I/D polymorphism is characterized by the presence (insertion) or absence (deletion) of a 288-base pair alu repeat sequence within intron 16, which results in the following 3 genotypes: II and DD homozygotes and ID heterozygotes. As suggested by the results of a combined segregation and linkage analysis, a functional mutation, located within or close to the ACE gene and being in strong linkage disequilibrium with the I/D site, is responsible for plasma ACE activity.

ACE is involved in coronary thrombosis, vasoconstriction, and smooth muscle cell proliferation. High levels of ACE may increase the risk of coronary thrombosis through the enhanced production of plasminogen activator inhibitor-1. ACE also interferes with coronary vasomotion, and high plasma ACE levels may lead to increased arterial wall thickness. These effects may be relevant to the pathophysiology of coronary artery disease, myocardial infarction, and restenosis after percutaneous coronary interventions. However, the conflicting results attained so far do not allow for the definitive establishment of the role of the I/D polymorphism of the ACE gene. Although studies that found a positive association between this polymorphism and myocardial infarction, this association is not always confirmed. A similar controversy also exists for coronary artery disease, with a number of studies providing either positive or negative evidence about the association of the disease with the ACE I/D polymorphism. After the first report on the association of the I/D polymorphism with restenosis after coronary balloon angioplasty, this finding could not be confirmed by more recent studies.

Intracoronary stent placement is an established treatment strategy for coronary artery disease. Substantial differences

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exist in the mechanisms of restenosis between conventional coronary angioplasty and stenting. Although arterial remodeling is the main contributor to lumen narrowing after percutaneous transluminal coronary angioplasty, neointimal hyperplasia is almost exclusively the mechanism of restenosis after stenting, and the I/D polymorphism may play a major role in this setting. In fact, recent studies performed in limited series of selected patients with coronary stenting reported a positive relation between ACE I/D polymorphism and restenosis.

The present study was designed to determine whether the D allele of the ACE gene was associated with a higher risk of restenosis after coronary stent placement in a large population of patients.

**Methods**

**Patients**
The study included 1850 consecutive white patients with symptomatic coronary artery disease who underwent coronary stent implantation at the Deutsches Herzzentrum München and 1. Medizinische Klinik rechts der Isar der Technischen Universität München. All patients gave written informed consent for the intervention, routine follow-up angiography at 6 months, and ACE I/D genotype determination. The study protocol conformed to the Declaration of Helsinki and was approved by the institutional ethics committee. The protocol of stent placement and poststent therapy is described in detail elsewhere. Most of the stents were implanted using a small, hand-mounted angioplasty balloon. Postprocedural therapy consisted of aspirin (100 mg twice daily, indefinitely) and ticlopidine (250 mg twice daily for 4 weeks). Patients who were considered at a higher risk for stent thrombosis received additional therapy with abciximab, which was given as a bolus injection during the stent insertion procedure and as a 12-hour continuous infusion thereafter. The decision to give abciximab was made at the operator’s discretion.

**Determination of the ACE I/D Genotype**
Genomic DNA was extracted from peripheral blood leukocytes. A portion of intron 16 and a portion of exon 17 of the ACE gene were amplified by polymerase chain reaction using the method of Rigat et al. The presence (allele I) or absence (allele D) of the 288-bp alu repeat sequence was determined by evaluating the size of the DNA products (479 bp for allele I and 191 bp for allele D). The possibility of mistyping ID heterozygotes as DD homozygotes due to the preferential amplification of the smaller D allele was addressed. All samples typed as DD homozygotes were subjected to a second, independent polymerase chain reaction with a primer pair that permits amplification only in the presence of the I allele but not the D allele; this was done using the method described by Lindpaintner et al. The operators who performed the I/D genotype determination were unaware of the patients’ clinical and angiographic characteristics.

**Angiographic Assessment**
Lesions were classified according to the modified American College of Cardiology/American Heart Association grading system. A quantitative computer-assisted angiographic analysis was performed off-line on angiograms obtained just before stenting, and at follow-up using the automated edge-detection system CMS (Medis Medical Imaging Systems). Operators were unaware of the patients’ genotype. Identical projections of the target lesion were used for all assessed angiograms. Minimal lumen diameter, interpolated reference diameter, percent diameter stenosis, lesion length, and the diameter of the maximally inflated balloon were the angiographic parameters obtained with this analysis system. Late lumen loss was calculated as the difference between minimal lumen diameter at the time of follow-up angiography. Loss index was calculated as the ratio between late lumen loss and acute lumen gain.

**Definitions and Study End Points**
Death from any cause, myocardial infarction, and target vessel revascularization (balloon angioplasty or aortocoronary bypass surgery) were considered major adverse cardiac events. The diagnosis of acute myocardial infarction was based on the criteria applied in the Evaluation of Platelet IIa/IIIb Inhibitor for Stenting (EPISTENT) trial (new pathological Q waves or a value of creatine kinase or its MB isoenzyme ≥ 3 times the upper limit). Creatine kinase was determined systematically over the 48 hours after the stenting procedure. Target vessel revascularization was considered if angiographic restenosis plus anginal symptoms or objective signs of ischemia were present. 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, as well as a control angiography at 6 months.

The primary end point of the study was restenosis, which was defined as a diameter stenosis ≥ 50% at follow-up angiography. The secondary end point of the study was the 1-year clinical outcome. The incidence of adverse clinical events during the first 30 days after stenting was also separately assessed.

The sample size of the study was chosen to provide the analysis with a 80% power (α error of 0.05) to detect an increase in the restenosis rate from 27% (as assumed in the group of patients with genotype II) to 35% (as assumed in the group of patients with genotypes ID and DD) and to accommodate a missing follow-up angiography rate of ≤ 20%.

**Statistical Analysis**
Discrete variables are expressed as counts or percentages; they were compared with χ² or Fisher’s exact test, as appropriate. Continuous variables are expressed as mean ± SD and compared by means of the unpaired, 2-sided t test or ANOVA for > 2 groups. The Kaplan-Meier method and the log-rank test were used to compare 1-year event-free survival between the groups with different I/D genotypes. Post-hoc tests with a correction for multiple comparisons were performed only when the overall test yielded a significant difference.

The independent association between the presence of the D allele and outcome was assessed after adjusting for other potential confounding factors using multiple logistic regression analysis for restenosis and the Cox proportional hazards model for event-free survival. All variables associated with a P<0.1 in univariate analysis were entered into the multivariate model as covariates. Three different multivariate models were constructed in accordance with the assumed genetic effect of the D allele. The model in which a dominant effect for the D allele was assumed contained genotype II coded as 0 and genotypes ID and DD coded as 1. The model in which a recessive effect for the D allele was assumed contained genotype II coded as 0, genotype ID coded as 1, and genotype DD coded as 2. All statistical analyses were performed using S-Plus software (Mathsoft, Inc). Statistical significance was accepted at P<0.05.

**Results**

**Patient Characteristics**
The ACE genotype was II in 395 patients (21.3%), ID in 949 patients (51.3%), and DD in 506 patients (27.4%). Thus, D allele frequency was 0.53. The ACE genotype distribution was in Hardy-Weinberg equilibrium. The main baseline characteristics of the patients are listed in Table 1. DD patients were older, included a greater proportion of women, and were more likely to have diabetes, unstable angina, and multivessel disease. The angiographic and procedural characteristics at the time of intervention are listed in Table 2. The
lesions of patients with the DD genotype tended to be longer and were more often situated in bypass grafts. Table 3 displays the major events that occurred during the first 30 days after stent placement. No significant differences existed between the 3 genotypes.

Primary End Point Analysis
Six-month follow-up angiography was performed in 1556 patients (84%). The proportion of patients with control angiography at 6 months was not significantly different between the 3 groups; it was 83.3% in II patients, 84.7% in ID

### Table 2. Lesion and Procedural Characteristics at the Time of Intervention

<table>
<thead>
<tr>
<th></th>
<th>II (n=395)</th>
<th>ID (n=949)</th>
<th>DD (n=506)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessels</td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Left main</td>
<td>6 (1.5)</td>
<td>13 (1.4)</td>
<td>8 (1.6)</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>176 (44.6)</td>
<td>366 (38.6)</td>
<td>192 (37.9)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>72 (18.2)</td>
<td>207 (21.8)</td>
<td>90 (17.8)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>118 (29.9)</td>
<td>308 (32.4)</td>
<td>170 (33.6)</td>
<td></td>
</tr>
<tr>
<td>Venous bypass graft</td>
<td>23 (5.8)</td>
<td>55 (5.8)</td>
<td>46 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Chronic occlusions</td>
<td>33 (8.4)</td>
<td>59 (6.2)</td>
<td>26 (5.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Complex lesions</td>
<td>304 (77.0)</td>
<td>706 (74.4)</td>
<td>371 (73.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Restenotic lesions</td>
<td>98 (24.8)</td>
<td>234 (24.7)</td>
<td>117 (23.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>Before stenting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>3.03±0.51</td>
<td>3.02±0.53</td>
<td>3.07±0.55</td>
<td>0.22</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>0.66±0.51</td>
<td>0.63±0.49</td>
<td>0.64±0.49</td>
<td>0.69</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>11.4±6.5</td>
<td>12.3±6.8</td>
<td>12.1±6.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Procedural data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>13.8±3.3</td>
<td>13.8±3.3</td>
<td>14.0±3.3</td>
<td>0.61</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.07±0.10</td>
<td>1.07±0.10</td>
<td>1.07±0.09</td>
<td>0.52</td>
</tr>
<tr>
<td>Stented segment length, mm</td>
<td>20.0±13.8</td>
<td>20.2±14.3</td>
<td>20.2±13.4</td>
<td>0.89</td>
</tr>
<tr>
<td>Immediately after stenting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>2.89±0.53</td>
<td>2.92±0.50</td>
<td>2.97±0.54</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are No. of patients (%) or mean±SD. LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; and RCA, right coronary artery. Complex lesions were defined as lesion types B2 and C according to the American College of Cardiology/American Heart Association grading system.
patients, and 83.6% in DD patients \( (P=0.76) \). The quantitative angiographic results are presented in Table 4. The restenosis rate at angiographic follow-up was 32.8% for II patients, 34.0% for ID patients, and 31.2% for DD patients \( (P=0.62) \). In a multivariate analysis of restenosis (logistic regression), we adjusted for age, sex, arterial hypertension, diabetes, current smoking habit, unstable angina, multivessel disease, vessel location, lesion length, and postprocedural minimal lumen diameter. The adjusted odds ratios were 1.01 \( (95\% \text{ confidence interval, } 0.77 \text{ to } 1.32) \) for DD/ID patients versus II patients, 0.92 \( (95\% \text{ confidence interval, } 0.72 \text{ to } 1.18) \) for DD patients versus II/ID patients, and 0.94 \( (95\% \text{ confidence interval, } 0.69 \text{ to } 1.29) \) for DD patients versus II patients.

**Secondary End Point Analysis**

Complete clinical follow-up data were available for all patients, irrespective of the presence or absence of control angiography. Event-free survival 1 year after stent placement (survival free of myocardial infarction and target vessel revascularization) was 77.7% in patients with genotype II, 75.2% in patients with genotype ID, and 75.5% in patients with genotype DD \( (P=0.54) \). One-year survival free of myocardial infarction was 94.9% in patients with genotype II, 93.0% in patients with genotype ID, and 94.7% in patients with genotype DD \( (P=0.30) \). Overall survival 1 year after stent placement was 98.2% in patients with genotype II, 96.9% in patients with genotype ID, and 98.0% in patients with genotype DD \( (P=0.27) \). Even after adjusting for other factors, as in the case of restenosis, the presence of the D allele was not associated with any significant increase in the risk for an adverse outcome at 1 year.

**Subgroup Analysis**

The incidence of both restenosis and event-free survival was calculated in different subsets of patients, such as patients <60 years, male patients, patients without acute myocardial infarction, patients not treated with abciximab, and patients who did not receive ACE inhibitors. These subgroup analyses also failed to show any significant influence of the ACE I/D genotype. Of note, among 341 patients with a low risk for restenosis (defined as patients without diabetes who had lesions <15 mm situated in vessels ≥3 mm in size and treated with a single stent), the incidence of restenosis was 21.7% in II carriers, 23.4% in ID carriers, and 19.7% in DD carriers \( (P=0.83) \).

**Discussion**

The issue of the influence of the I/D polymorphism of the ACE gene on cardiovascular risk has remained largely unresolved, despite the plethora of work on this topic. This primarily reflects the complexity of polygenic, multifactorial diseases.\textsuperscript{24} Another explanation for the existing controversy on this issue can be found in the meta-analysis of Samani et al,\textsuperscript{25} which documented the inverse correlation between study population size and magnitude of relative risk associated with I/D polymorphism. We tried to resolve these concerns through the design of this prospective study. We included a large and consecutive population of patients with coronary stent placement, and we combined clinical and quantitative angiographic measures to better assess the outcome of these patients over a period that was long enough for the potential prothrombotic and prorestenotic effects of the I/D polymorphism to become clinically evident. During the assessment of the risk associated with this polymorphism, we took into account the multifactorial nature of the processes under scrutiny (thrombosis and restenosis) and performed due adjustments using multivariate models.

Interestingly, the D allele homozygotes presented with a higher risk profile: these patients were more likely to be female, they were older, and they were more likely to have

**TABLE 3. Major Adverse Events During the Early 30-Day Period After Intervention**

<table>
<thead>
<tr>
<th>Event</th>
<th>II (n=395)</th>
<th>ID (n=949)</th>
<th>DD (n=506)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (0.5)</td>
<td>12 (1.3)</td>
<td>3 (0.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>10 (2.5)</td>
<td>29 (3.1)</td>
<td>16 (3.2)</td>
<td>0.84</td>
</tr>
<tr>
<td>Q-wave</td>
<td>7 (1.8)</td>
<td>7 (0.8)</td>
<td>3 (0.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Non-Q-wave</td>
<td>3 (0.8)</td>
<td>22 (2.3)</td>
<td>13 (2.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>10 (2.5)</td>
<td>21 (2.2)</td>
<td>18 (3.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>Any of the above events</td>
<td>17 (4.3)</td>
<td>51 (5.4)</td>
<td>29 (5.7)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Data are No. of patients (%).*

**TABLE 4. Results of Follow-Up Angiography According to ACE Genotype**

<table>
<thead>
<tr>
<th>Measure</th>
<th>II (n=329)</th>
<th>ID (n=804)</th>
<th>DD (n=423)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>1.70±0.93</td>
<td>1.73±0.93</td>
<td>1.77±0.93</td>
<td>0.60</td>
</tr>
<tr>
<td>Late lumen loss, mm</td>
<td>1.20±0.85</td>
<td>1.20±0.83</td>
<td>1.21±0.86</td>
<td>0.97</td>
</tr>
<tr>
<td>Loss index</td>
<td>0.58±0.45</td>
<td>0.55±0.40</td>
<td>0.56±0.42</td>
<td>0.62</td>
</tr>
<tr>
<td>Restenosis</td>
<td>108 (32.8)</td>
<td>273 (34.0)</td>
<td>132 (31.2)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*Data are mean±SD or No. of patients (%).*
diabetes, multivessel disease, and unstable angina. This study was not designed to investigate the potential relation between ACE genotype and cardiovascular risk profile. On the basis of previous findings, however, diabetic patients with the DD genotype are at an increased risk of vascular complications, which may explain, at least in part, the differences in baseline characteristics verified in our population.

The main finding of the study is that the ACE gene I/D polymorphism is not associated with any appreciable increase in the risk for thrombosis- and restenosis-driven adverse events in patients undergoing coronary stent placement. These data are in line with the previous lack of association found between this polymorphism and restenosis after balloon angioplasty. However, in 146 patients who received coronary stent placement mostly due to complications or suboptimal results after conventional angioplasty, Amant et al. found an association between the presence of the D allele and angiographic restenosis that was compatible with the assumption of a codominant effect for this allele. Similar angiographic findings were recently reported by Ribichini et al. in 176 selected patients with stent placement who had to fulfill several inclusion criteria. We do not know the exact reason for the difference between the results we achieved in a much larger series of patients and the above-mentioned results provided by relatively small series of selected subjects. The difference in population size is a likely explanation, but differences in baseline characteristics and study design may also offer additional reasons.

Some previous findings may serve to explain the lack of influence of I/D polymorphism on the risk for thrombotic and restenotic events after the coronary placement of stents, as shown in the present study. Although high levels of ACE may increase the production of plasminogen activator inhibitor-I, Jeng et al. did not find an association between I/D polymorphism and plasminogen activator inhibitor-I concentration. In addition, Girerd et al. did not find any relation between the wall thickness of the radial and carotid arteries and I/D polymorphism. Interesting data in support of our negative findings were recently reported in 104 patients who underwent coronary atherecromy and angiographic follow-up. The ACE content of the plaque removed during the procedure was not associated with I/D polymorphism, yet it was a strong predictor of restenosis. Therefore, the failure to find a significant influence of I/D polymorphism in our study does not constitute evidence against the possible involvement of the renin-angiotensin system in neointimal hyperplasia and restenosis after stent placement.

Limitations
This study was performed in white patients only, and the lack of other racial groups may limit the generalizability of the findings. We achieved an 84% reangiography rate at 6 months. The I/D genotype of the patients without angiographic follow-up was not different from that of the patients with control angiography. In addition, all patients had clinical follow-up, which attenuates the impact of the missing angiographic restudy. The overall incidence of restenosis of 33.0% reflects the unselected nature of the population included in this study. However, a subgroup analysis in 341 patients with low-risk characteristics and a restenosis rate of 22%, comparable to that observed in the studies of Amant et al. and Ribichini et al., also indicated that the ACE genotype did not have a measurable influence on restenosis. Another limitation may be related to the observed differences in baseline characteristics among the ACE I/D genotypes and to the potential bias these differences may have introduced in our restenosis analysis. A significant bias is unlikely for 2 reasons. (1) We adjusted for baseline differences by multivariate analysis and found no relation between restenosis and ACE I/D genotype after adjustment. (2) The lack of an increased risk of restenosis with D allele carriage as shown in this study may not be attributed to the differences in baseline characteristics because DD patients presented more frequently with diabetes, multivessel disease, and unstable angina, factors that are usually associated with a higher risk for restenosis.

Conclusions
The ACE DD genotype or D allele does not influence the 1-year clinical and angiographic outcome of patients undergoing coronary stent placement. These data suggest that routine determination of the ACE genotype may not help identify patients who are at higher risk of thrombotic and restenotic events after coronary stent placement.

References
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