Apolipoprotein E gene polymorphisms and thrombosis and restenosis after coronary artery stenting

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Abstract Experimental data support a protective function of apolipoprotein E (apoE) against restenosis, the main factor limiting the long-term benefit of percutaneous coronary interventions. We investigated the possibility that the single nucleotide polymorphisms (SNPs) –219G/T, 113G/C, 334T/C, and 472C/T of the gene encoding apoE (APOE) are associated with the incidence of death and myocardial infarction or restenosis after stenting in coronary arteries. In addition, we asked whether the apoE isotype-related ε2/ε3/ε4 polymorphism, defined by specific allele combinations (haplotypes) of the 334T/C and 472C/T polymorphism, and other APOE haplotypes, derived from all four SNPs investigated, are associated with adverse clinical and angiographic outcomes after stenting. Our study included 1,850 consecutive patients with symptomatic coronary artery disease (CAD) who underwent stent implantation. Follow-up angiography was performed in 1,556 patients (84.1%) at 6 months after the intervention. We found that none of the APOE SNPs is associated with death and myocardial infarction or restenosis after stenting. In addition, we observed no relationship between APOE haplotypes and adverse outcomes. In conclusion, the APOE –219G/T, 113G/C, 334T/C, and 472C/T polymorphisms, either alone or in combination, do not represent genetic markers of the risk of thrombotic and restenotic complications in patients with CAD treated with coronary stenting.


Supplementary key words coronary artery disease • APOE ε alleles • APOE haplotypes • TaqMan genotyping

Compared with conventional balloon angioplasty, stenting has improved the outcome of patients with coronary artery disease (CAD) (1). However, restenosis remains the principal factor limiting the long-term benefit of stenting (1). Experimental data have pointed to a protective function of apolipoprotein E (apoE) against restenosis (2–4). ApoE was found to inhibit cell signaling events associated with growth factor-induced smooth muscle cell migration and proliferation and to limit neointimal hyperplasia after arterial injury (2, 3). These results correspond to the observation that deficiency of apoE was associated with increased neointima formation after endothelial denudation (3, 4).

The apoE gene (APOE) is polymorphic, and some of its allelic forms are known to differentially affect transcriptional activity or give rise to structurally and functionally distinct protein isoforms (5–8). Evidence exists to suggest that the variability of APOE has differential effects on the atheroprotective potential attributed to apoE (5, 6). The ε2/ε3/ε4 polymorphism of APOE is caused by two single nucleotide polymorphisms (SNPs), 334T/C and 472C/T, which are in close physical proximity and absolute linkage disequilibrium (5, 9). The 334T/C and 472C/T SNPs exclusively determine three haplotypes, known as the ε2 (334T/472T), ε3 (334C/472T), and ε4 (334C/472C) alleles of APOE (5). This heterogeneity causes variation at amino acid positions 112 (cysteine or arginine) and 158 (arginine or cysteine) of apoE, resulting in three different isoforms of apoE (5). The ε2/ε3/ε4 polymorphism is one of the most thoroughly studied polymorphisms, especially for its effects on lipid profiles and CAD risk (5, 6). This polymorphism was found to be relevant for apoE plasma level, receptor binding affinity of apoE, plasma lipid and lipoprotein concentrations, and CAD (5, 6). In particular, the 334C allele and the ε4 allele were observed to impose an increased risk of CAD (5, 10), and, among patients with CAD, the ε4 allele was related to more severe and the ε2 allele was related to less severe disease (11). The presence of the ε4 allele has been associated with increased death rates in patients with CAD (12, 13). The cardiovascular risk attributed to the ε4 allele may be related to, at

Abbreviations. apoE, apolipoprotein E; APOE, gene encoding apolipoprotein E; CAD, coronary artery disease; CI, confidence interval; SNP, single nucleotide polymorphism.

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least in part, a lower antioxidant activity of the apoE4 iso-
form (112Arg/158Arg) compared with that of the apoE2 iso-
form (112Cys/158Cys) or the apoE3 isoform (112Cys/
158Arg) (14). Another SNP of APOE, −219G/T, located in
the promoter of APOE, was reported to be significantly
associated with APOE promoter activity, apoE plasma con-
centration, and CAD (7, 8, 10). In addition, the 113G/C
SNP of APOE may be relevant for APOE regulation be-
cause of its location in the APOE intron-1 enhancer ele-
ment that constitutes a binding site for specific nuclear
protein factors (15, 16).

Together, a number of findings suggest a significant im-
pact of apoE and genetic variants of APOE on cardiovas-
cular risk. APOE polymorphisms may also be associated
with angiographic and clinical outcomes after subcutane-
ous interventions in coronary arteries. Inconsistent re-
sults were obtained regarding the relationship between
the e2/e3/e4 polymorphism and restenosis after balloon
angioplasty in coronary arteries (17–20). It has not been
even examined whether the APOE −219G/T, 113G/C, 334T/C,
and 472C/T SNPs, or APOE haplotypes based on the e2/
e3/e4 polymorphism, or combinations of all four SNPs
are related to thrombotic and restenotic complications af-
ter coronary stenting. We addressed this issue in a study
that included a relatively large and consecutive series of
patients with CAD.

PATIENTS AND METHODS

Patients

The study included a consecutive series of 1,850 Caucasian pa-
tients with symptomatic CAD who underwent stent implantation
at Deutsches Herzzentrum München and 1. Medizinische Klinik
rechts der Isar der Technischen Universität München. The proto-
colos of stent placement and poststenting therapy were described in
detail elsewhere (21, 22). Postprocedural pharmacologic ther-
apy 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 ischemic complications received
additional therapy with the glycoprotein IIb/IIIa blocker abic-
iximab, which was given as a bolus injection during the stent inser-
tion procedure and as a 12 h continuous infusion thereafter. All
patients were scheduled for angiographic follow-up at 6 months.
Written informed consent was obtained from the patients for the
intervention, follow-up angiography, and genotype determina-
tion. The study protocol was approved by the Institutional Ethics
Committee, and the reported investigations were in accordance
with the principles of the current version of the Declaration of
Helsinki.

ApoE genotyping

Genotyping of the APOE −219G/T, 113G/C, 334T/C, and
472C/T SNPs was performed with TaqMan assays, as previously
described (9).

Angiographic evaluation

Lesion morphology was classified according to the modified
American College of Cardiology/American Heart Association
grading system in type A, B1, B2, and C; lesions of types B2 and C
were considered complex lesions. Angiograms were recorded
just before and immediately after the intervention and at 6
month follow-up. Matched projections of the target lesions were
selected for quantitative computer-assisted off-line analysis of the
angiograms with the automated edge-detection system CMS (Me-
dis Medical Imaging Systems, Nuenen, The Netherlands). The
angiographic parameters obtained were interpolated reference
diameter, lesion length, diameter stenosis before and after stent-
ing and at follow-up, diameter of the maximally inflated balloon
during stent placement, and length of the stented segment. Quan-
titative analysis of angiograms was performed by operators not in-
volved in the stenting procedure and unaware of the laboratory
or genetic data.

Definitions and study end points

The primary end point of the study was restenosis. Two defini-
tions of restenosis were used: the incidence of a diameter steno-
sis of ≥50% at 6 month follow-up angiography (angiographic
restenosis) and the need for target vessel revascularization (per-
cutaneous transluminal coronary balloon angioplasty or aorto-
coronary bypass grafting) as a result of symptoms or signs of isch-
emia in the presence of angiographic restenosis at the stented
site within 1 year after stent placement (clinical restenosis). A
secondary end point was the combined incidence of all-cause
death and nonfatal myocardial infarction at 1 year after stenting.
The diagnosis of acute myocardial infarction was based on the
presence of new pathological Q waves on the electrocardiogram
or a value of creatine kinase or its MB isoenzyme at least three
times the normal upper limit.

Statistical analysis

Determination of haplotypes and haplotype frequencies was
performed with the expectation-maximization (EM) algorithm
and the Markov chain-Monte Carlo algorithm, as previously de-
scribed (9). Discrete variables are expressed as counts and per-
centages and were compared with the Chi-square test or the Fisher
exact test, as appropriate. Continuous variables are expressed as
means ± SD and were compared by means of the unpaired, two-
sided t-test or ANOVA for more than two groups. We tested for
independent association of the APOE SNP-related genotypes and
haplotype-related genotypes in multivariate models (multiple lo-
gistic regressions) of restenosis that included age, gender, arte-
rial hypertension, hypercholesterolemia, current tobacco smok-
ing, diabetes mellitus, unstable angina pectoris, acute myocardial
infarction, previous myocardial infarction, previous bypass sur-
gery, target coronary vessel, lesion complexity, ostial lesion, chronic
occlusion, restenotic lesion, multivessel disease, reference diam-
eter, lesion length, diameter stenosis before stenting, balloon-
to-vessel ratio, maximal balloon pressure, length of the stented
segment, diameter stenosis after stenting, and abciximab therapy
as potentially confounding factors. Adjusted odds ratios and 95%
Wald confidence intervals (CIs) were calculated on the basis of the
multiple logistic regression models. Analyses were performed
using the S-Plus statistical package (Mathsoft, Inc., Seattle, WA).

RESULTS

Patient characteristics

We determined the genotypes of the −219G/T, 113G/C,
334T/C, and 472C/T SNPs of APOE in 1,850 patients
with CAD who underwent stenting in coronary arteries.
The distributions of the genotypes were 27.1% −219GG,
48.5% −219GT, 24.3% −219TT, 41.0% 113GG, 44.9% 113GC,
14.1% 113CC, 73.7% 334TT, 24.0% 334TC, 2.3% 334CC,
and 86.8% 472CC, 12.4% 472CT, 0.8% 472TT. For comparisons with the carriers of the abundant 334TT and 472CC genotypes, patients with the rare 334CC and 472TT genotypes were combined with the patients who carried the 334TC and 472CT genotypes, respectively. Patients with the 334TC and 334CC genotypes represented the carriers of the APOE ε4 allele, and patients with the 472CT and 472TT genotypes represented the carriers of the APOE ε2 allele. Table 1 shows baseline clinical characteristics, lesion-related variables before stenting, and procedural parameters of the patients in relation to the genotypes of the APOE SNPs. We observed no statistically significant differences between the groups, with the following exceptions: i) patients with the −219GT genotype were younger than the carriers of the −219GG or −219TT genotype (P = 0.04); ii) reference diameter increased with the number of 113G alleles (P = 0.006); iii) in patients with the 334TT genotype, hypercholesterolemia (P = 0.04), acute myocardial infarction (P = 0.03), and periprocedural treatment with abciximab (P = 0.03) were

| Table 1. Baseline clinical characteristics, lesion variables before stenting, and procedural parameters according to the genotypes of the APOE−219G/T, 113G/C, 334T/C, and 472C/T SNPs (n = 1,850) |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Variable                 | −219G/T                 | 113G/C                   | 334T/C                   | 472C/T                   |
|                         | (n = 502)               | (n = 898)                | (n = 540)                | (n = 1,363)              |
| Age (years)             | 63.6 ± 10.1             | 62.4 ± 10.0              | 63.6 ± 9.9               | 63.0 ± 9.9               |
| Women (n)               | 112 (22.3)              | 174 (19.4)               | 105 (23.5)               | 158 (20.8)               |
| Arterial hypertension   | 336 (66.9)              | 614 (68.4)               | 309 (68.7)               | 510 (67.2)               |
| Hypercholesterolemia    | 214 (42.6)              | 386 (43.0)               | 192 (42.7)               | 341 (44.9)               |
| Current smoking         | 146 (29.1)              | 289 (32.2)               | 135 (30.0)               | 254 (30.8)               |
| Diabetes mellitus       | 102 (20.5)              | 191 (21.3)               | 95 (21.1)                | 149 (19.0)               |
| Unstable angina pectoris| 132 (26.3)              | 245 (27.3)               | 138 (30.7)               | 204 (26.9)               |
| Acute myocardial infarction| 98 (19.5)            | 184 (20.5)               | 93 (20.7)                | 159 (20.9)               |
| Bypass surgery          | 57 (11.4)               | 91 (10.1)                | 57 (12.7)                | 88 (11.6)                |
| Target coronary vessel  | 8 (1.6)                 | 13 (1.5)                 | 6 (1.3)                  | 10 (1.3)                 |
| Left main coronary artery| 94 (18.7)              | 177 (19.7)               | 98 (21.8)                | 147 (19.4)               |
| Left circumflex coronary artery| 210 (41.8)       | 351 (39.1)               | 173 (38.4)               | 307 (40.5)               |
| Right coronary artery   | 159 (31.7)              | 300 (33.4)               | 137 (30.4)               | 240 (31.6)               |
| Venous bypass graft     | 31 (6.2)                | 77 (6.4)                 | 36 (8.0)                 | 55 (7.3)                 |
| Complex lesion (ACC/AHA type) | 379 (75.5)       | 655 (72.9)               | 347 (77.1)               | 570 (75.1)               |
| B2 or C                 | 36 (7.2)                | 64 (7.1)                 | 27 (6.0)                 | 51 (6.7)                 |
| Chronic occlusion       | 40 (8.0)                | 49 (5.5)                 | 29 (6.4)                 | 57 (7.5)                 |
| Restenotic lesion       | 133 (26.5)              | 213 (23.7)               | 103 (22.9)               | 200 (26.4)               |
| Multivessel disease     | 365 (72.7)              | 645 (71.8)               | 315 (70.7)               | 547 (72.1)               |
| Reference diameter (mm) | 3.06 ± 0.53             | 3.04 ± 0.52              | 3.00 ± 0.56              | 3.08 ± 0.53              |
| Lesion length (mm)      | 12.2 ± 6.9              | 12.1 ± 6.7               | 12.3 ± 6.8               | 12.0 ± 6.6               |
| Diameter stenosis (%)   | 79.2 ± 15.7             | 78.2 ± 15.2              | 80.0 ± 14.9              | 79.1 ± 15.5              |
| Balloon-to-vessel ratio | 1.07 ± 0.09             | 1.07 ± 0.10              | 1.07 ± 0.10              | 1.07 ± 0.11              |
| Maximal balloon pressure | 13.9 ± 3.2             | 13.8 ± 3.4               | 13.9 ± 3.2              | 13.8 ± 3.3               |
| Stented segment length (mm) | 20.2 ± 14.8         | 20.2 ± 13.8              | 20.0 ± 13.2              | 20.6 ± 14.8              |
| Diameter stenosis (%)   | 5.2 ± 7.7               | 5.3 ± 9.1                | 5.4 ± 7.4               | 5.5 ± 9.2                |
| Periprocedural abciximab therapy | 90 (17.9)           | 183 (20.4)               | 91 (20.2)                | 148 (19.5)               |

Data are presented as mean values ± SD or the number (%) of patients, ACC/AHA, American College of Cardiology/American Heart Association grading system; APOE, gene encoding apolipoprotein E (apoE); SNP, single nucleotide polymorphism.
less frequent and diabetes mellitus ($P = 0.04$) was more frequent than among carriers of the 334C allele (334TC genotype or 334CC genotype).

The apoE isotype-related genotypes $e2e2$, $e2e3$, $e2e4$, $e3e3$, $e3e4$, and $e4e4$ were present at 0.8, 11.2, 1.2, 61.7, 22.8, and 2.3%, respectively. Genotype-based evaluation revealed that the allelics of the four APOE SNPs were arranged in eight different haplotypes: haplotype 1 $= \text{–}219G/113G/334T/472T$ (GGTT; 7.0%), haplotype 2 $= \text{G}GT\text{C}$ (41.6%), haplotype 3 $= \text{TCTC}$ (36.3%), haplotype 4 $= \text{TGTC}$ (0.6%), haplotype 5 $= \text{GTGC}$ (0.2%), haplotype 6 $= \text{GGCC}$ (11.7%), haplotype 7 $= \text{GGCC}$ (2.6%), and haplotype 8 $= \text{TGCC}$ (< 0.001%). Haplotype 1 was the only haplotype that represented the $e2$ allele (334T/472T); haplotypes 2–5 included the $e3$ allele (334T/472C); and haplotypes 6–8 contained the $e4$ allele (334C/472C). It was possible to assign a genotype, defined by a specific combination of two of the eight haplotypes, to each patient. In total, 23 different haplotype-related genotypes were present in the study population.

**Clinical and angiographic outcomes**

Follow-up angiography of coronary arteries was performed in 1,556 (84.1%) of the patients 6 months after stenting. The proportions of the patients who underwent 6 month angiography were not substantially different among the SNP-related genotype groups ($P \geq 0.60$), apoE isotype-related genotypes ($P \geq 0.80$), and other haplotype-related genotypes ($P \geq 0.63$). Complete 1 year clinical follow-up data were available for all patients, irrespective of the presence or absence of follow-up angiography.

**APOE SNP-related genotypes**

The combined incidence of all-cause death and nonfatal myocardial infarction was not significantly different between patients with the –219GG, –219GT, and –219TT genotypes ($P = 0.76$), patients with the 113GG, 113GC, and 113CC genotypes ($P = 0.78$), patients with the 334TT genotype and carriers of the 334C allele ($e4$ allele carriers) ($P = 0.21$), or patients with the 472CC genotype and carriers of the 472T allele ($e2$ allele carriers) ($P = 0.75$) (Table 2).

**TABLE 2.** Death or myocardial infarction, clinical restenosis, and angiographic restenosis according to the genotypes of the APOE –219G/T, 113G/C, 334T/C, and 472T/C SNPs

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>Death or Myocardial Infarction</th>
<th>Clinical Restenosis</th>
<th>n</th>
<th>Angiographic Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>–219 GG</td>
<td>502</td>
<td>34 (6.8) (100 (19.9)</td>
<td>420</td>
<td>147 (35.0)</td>
<td></td>
</tr>
<tr>
<td>–219 GT</td>
<td>898</td>
<td>55 (5.8) (162 (18.0)</td>
<td>753</td>
<td>245 (32.5)</td>
<td></td>
</tr>
<tr>
<td>–219 TT</td>
<td>450</td>
<td>27 (6.0) (65 (14.4)</td>
<td>383</td>
<td>121 (31.6)</td>
<td></td>
</tr>
<tr>
<td>113GG</td>
<td>759</td>
<td>45 (5.9) (142 (18.7)</td>
<td>655</td>
<td>205 (32.3)</td>
<td></td>
</tr>
<tr>
<td>113GC</td>
<td>831</td>
<td>54 (6.5) (146 (17.6)</td>
<td>701</td>
<td>240 (34.2)</td>
<td></td>
</tr>
<tr>
<td>113CC</td>
<td>260</td>
<td>14 (5.4) (39 (15.0)</td>
<td>220</td>
<td>68 (30.9)</td>
<td></td>
</tr>
<tr>
<td>334TT</td>
<td>1,263</td>
<td>89 (6.5) (245 (18.0)</td>
<td>1,145</td>
<td>391 (34.1)</td>
<td></td>
</tr>
<tr>
<td>334TC + 334CC</td>
<td>487</td>
<td>24 (4.9) (82 (16.8)</td>
<td>411</td>
<td>122 (29.7)</td>
<td></td>
</tr>
<tr>
<td>472CC</td>
<td>1,606</td>
<td>97 (6.0) (277 (17.2)</td>
<td>1,353</td>
<td>439 (32.4)</td>
<td></td>
</tr>
<tr>
<td>472CT + 472TT</td>
<td>244</td>
<td>16 (6.6) (50 (20.5)</td>
<td>203</td>
<td>74 (36.5)</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 3.** Death or myocardial infarction, clinical restenosis, and angiographic restenosis according to apoE isotype-related genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>Death or Myocardial Infarction</th>
<th>Clinical Restenosis</th>
<th>n</th>
<th>Angiographic Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>$e2e2$</td>
<td>15</td>
<td>1 (6.7)</td>
<td>2 (13.3)</td>
<td>13</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>$e2e3$</td>
<td>207</td>
<td>15 (7.2)</td>
<td>45 (21.7)</td>
<td>170</td>
<td>64 (37.7)</td>
</tr>
<tr>
<td>$e2e4$</td>
<td>22</td>
<td>0</td>
<td>3 (13.6)</td>
<td>20</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>$e3e3$</td>
<td>1,141</td>
<td>73 (6.4)</td>
<td>198 (17.4)</td>
<td>962</td>
<td>322 (35.5)</td>
</tr>
<tr>
<td>$e3e4$</td>
<td>422</td>
<td>23 (5.5)</td>
<td>74 (17.5)</td>
<td>353</td>
<td>109 (30.9)</td>
</tr>
<tr>
<td>$e4e4$</td>
<td>43</td>
<td>1 (2.3)</td>
<td>5 (11.6)</td>
<td>38</td>
<td>8 (21.1)</td>
</tr>
</tbody>
</table>

Data are presented as number (%) of patients. $P = 0.17$ for all comparisons. Patients with the 334T and 334C genotypes represent carriers of the apoE isotype-related $e4$ allele, and patients with the 472CT and 472TT genotypes represent carriers of the $e2$ allele.

Similarly, the need for target vessel revascularization because of symptoms or signs of ischemia in the presence of angiographic restenosis at the stented site (clinical restenosis) was not substantially different among the genotype groups of the 219G/T ($P = 0.17$), 113G/C ($P = 0.52$), 334T/C ($P = 0.57$), and 472C/T ($P = 0.22$) SNPs (Table 2).

Angiographic restenosis rates were not significantly different between the genotype groups of the 219G/T ($P = 0.56$), 113G/C ($P = 0.59$), 334T/C ($P = 0.10$), and 472C/T ($P = 0.26$) SNPs (Table 2). Continuous measures of angiographic restenosis, diameter stenosis and loss index (the ratio of late lumen loss and acute lumen gain) were not substantially different between the genotype groups.

In a multivariate analysis of angiographic restenosis, we assessed the possible influence of baseline clinical characteristics, lesion-related variables, and procedural parameters on the relationship between the APOE SNPs and angiographic restenosis. After adjustment for these potentially confounding factors, the multivariate analysis did not reveal a significant independent association of the –219G/T ($P = 0.51$), 113G/C ($P = 0.45$), 334T/C ($P = 0.58$), or 472C/T ($P = 0.36$) SNP with angiographic restenosis; the adjusted odds ratios were 0.79 (95% CI 0.50–1.25), 1.18 (95% CI 0.77–1.79), 0.91 (95% CI 0.65–1.27), and 1.17 (95% CI 0.83–1.64), respectively.

**ApoE isotype-related genotypes and other APOE haplotype-related genotypes**

We evaluated the association of the six apoE isotype-related genotypes and the seven most frequent APOE haplotype-related genotypes, derived from four SNPs, with death and nonfatal myocardial infarction at 1 year, clinical restenosis, and angiographic restenosis. Patients who carried one of the seven frequent haplotype-related genotypes represented 89.9% of the total study population and 89.5% of the individuals with 6 month follow-up angiography. Data are shown in Table 3 (apoE isotype-related genotypes) and Table 4 (other haplotype-related genotypes). The combined incidence of all-cause death and nonfatal myocardial infarction was not significantly different be-
The incidence of restenosis after stenting in coronary arteries.

Haplotype-related genotypes based on the four SNPs are not significant (Table 4). Clinical restenosis rates were not substantially different between the apoE isotype-related genotype groups (Table 3) or other haplotype-related genotype groups (P = 0.95) (Table 4). Clinical restenosis rates were not substantially different between the apoE isotype-related genotype groups (P = 0.56) (Table 3) or other haplotype-related genotype groups (P = 0.97) (Table 4). No significant relationship existed between the frequency of the apoE isotype-related genotypes (P = 0.34) or other haplotype-related genotypes (P = 0.85) and angiographic restenosis (Tables 3, 4, respectively). The apparently lower rate of angiographic restenosis among the carriers of the e4/e4 genotype (21.1%) versus patients with the e2/e2 genotype (38.5%) (Table 3) was not significant (P = 0.21). Finally, multivariate analysis revealed no significant independent association of the apoE isotype-related genotypes (P = 0.52) or other haplotype-related genotypes (P = 0.87) with angiographic restenosis.

**DISCUSSION**

ApoE activities confer protection against various forms of vascular disease, including atherosclerosis and injury-induced restenosis (3, 4, 23, 24). Stent deployment elicits local inflammation and neointima formation (25, 26). ApoE is able to inhibit the proliferation of lymphocytes and vascular smooth muscle cells (2, 27) and, therefore, may interfere with the cascade of events that leads to restenosis. We asked whether ApoE polymorphisms with potential impact on APOE regulation or apoE function are suitable as predictors of clinical and angiographic outcomes after coronary stenting. The results presented here strongly suggest that the APOE-219G/T, 113G/C, 334T/C, and 472C/T SNPs, the e2/e3/e4 polymorphism, and APOE haplotype-related genotypes based on the four SNPs are not associated with death or myocardial infarction and the incidence of restenosis after stenting in coronary arteries.

The distribution of the apoE isotype-related genotypes in the present study cohort is in good agreement with the distribution of the corresponding apoE phenotypes in a Tyrolean population (28), and the genotype distribution of the -219G/T and 113G/C SNPs is similar to that observed in a study group from Spain (7).

Combined evidence suggested an association of the e4 allele with a higher cardiovascular risk than the e2 or e3 allele (5, 6, 8, 10–13, 17, 18). With regard to the clinical and angiographic outcomes after stenting, we observed no significant difference between patients who carried the e4 allele and patients who did not carry the e4 allele. The same was true when we compared patients with the e2 allele and patients without the e2 allele.

The association of the e2/e3/e4 polymorphism with restenosis after balloon angioplasty of coronary arteries has been observed (17, 18), but not in all studies that addressed this subject (19, 20). In the first of the positive reports (17), the e4 allele and e4/e4 genotype were significantly more prevalent among 59 patients with restenosis than among 91 patients who did not develop restenosis (P < 0.01 and P < 0.04, respectively). Similarly, in the second study with a positive finding (18), the e4/e4 genotype was present more often among 88 patients with restenosis than among 118 patients without restenosis (P < 0.05). Enrollment in these studies was restricted to patients who fulfilled several criteria, including the absence of acute myocardial infarction and previous balloon angioplasty or coronary bypass surgery (17, 18). We do not know the reason for the differences between the results we achieved in a much larger series of consecutive patients and the results reported in relatively small samples of selected patients (17, 18). The difference in population size may be an explanation, but differences in study design and baseline characteristics of the patients offer further reasons. In addition, the disparity may result from the fact that balloon angioplasty and stenting in coronary arteries provoke distinct vascular responses: restenosis after balloon angioplasty is characterized mainly by a remodeling process that results in shrinking of the artery (29); restenosis after stenting is caused primarily by neointimal hyperplasia caused by the proliferation of vascular smooth muscle cells and the accumulation of extracellular matrix (30). For this reason, the impact, if any, of the e2/e3/e4 polymorphism on the outcomes after balloon angioplasty and stenting may be different.

In conclusion, the present results suggest that the APOE-219G/T, 113G/C, 334T/C, and 472C/T SNPs, either alone or in combination, are not useful as indicators of adverse outcomes in patients who undergo stenting in coronary arteries.

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**REFERENCES**


