Letters

Observation

Peroxisome proliferator-activated receptor γ gene polymorphisms and restenosis in diabetic patients after stenting in coronary arteries

To the Editor: Although coronary artery stenting has been shown to reduce restenosis rates compared with balloon angioplasty, in-stent restenosis remains a significant clinical problem, especially in patients with diabetes mellitus [1]. Restenosis after stenting is mainly caused by exaggerated inflammatory reactions and neointima formation in response to mechanical injury of the arterial wall [2]. Combined evidence suggests that peroxisome proliferator-activated receptor γ (PPAR γ), a transcription factor structurally related to the nuclear receptors for steroid and thyroid hormones, attenuates the progress of atherosclerotic lesion development and restrains restenosis because of its inhibitory effects on inflammatory cell activation and vascular smooth muscle cell migration and proliferation [3, 4]. In support of this suggestion, it was reported that treatment of diabetic patients with the troglitazone, a PPAR γ activator, interferes with neointima formation after coronary artery stenting [5].

In a multiple-sample study on genetic associations of diabetes, a single nucleotide polymorphism of the PPAR γ gene, 34C/G, but none of the other candidate polymorphisms examined, was found to be associated with Type 2 diabetes [6]. The 34C/G polymorphism is located in exon B, which is exclusively used for the production of mRNA for the $\gamma 2$ isoform of PPAR γ (PPAR $\gamma 2$), and gives rise to a substitution of proline by alanine at amino acid position 12 of PPAR $\gamma 2$ (Pro12Ala) [7]. This polymorphism was shown to be related to differential insulin sensitivity, and to influence the binding affinity of PPAR $\gamma 2$ to the cognate promoter element as well as its ability to transactivate responsive promoters and target genes. A second single nucleotide polymorphism of the PPAR γ gene, 1431C/T, is located at nucleotide position 161 of exon 6, which is used for the synthesis of mRNA for the $\gamma 1$ and $\gamma 2$ isoforms of PPAR γ (1431 refers to the nucleotide position in the coding sequence for PPAR $\gamma 2$) [7]. Inconsistent findings were published on an association of the 1431C/T polymorphism with coronary artery disease.

Because of the potential importance of PPAR γ in diabetes and cardiovascular disease, we addressed the question of whether the 34C/G and 1431C/T polymorphisms of the PPAR γ gene are associated with restenosis and other major adverse events in diabetic patients treated with stenting in coronary

arteries. The study included 935 patients with diabetes mellitus and coronary artery disease who had undergone stent implantation. The study protocol was approved by the Institutional Ethics Committee and the reported procedures were in accordance with the Declaration of Helsinki. Diabetes mellitus was defined as the presence of an active treatment with insulin or with an oral antidiabetic agent. The patients were not treated with antidiabetic thiazolidinedione drugs, which are activators of PPAR γ [8]. All patients were scheduled for angiographic follow-up at 6 months. The primary endpoint of the study was restenosis. Two definitions of restenosis were used: (i) an incidence of diameter stenosis of $\geq 50\%$ at 6-month follow-up angiography (angiographic restenosis) and (ii) the need for target vessel revascularisation (percutaneous transluminal coronary balloon angioplasty or aorto-coronary bypass grafting) due to symptoms or signs of ischaemia in the presence of angiographic restenosis at the stented site over 1 year after stent placement (clinical restenosis). The secondary endpoint was the combined incidence of all-cause death and non-fatal myocardial infarction at 1 year after stenting. We separately assessed the incidence of thrombotic events during the early 30-day period after stenting that resulted in death, acute myocardial infarction or urgent target vessel revascularisation. The sample size of the study was chosen to provide the analysis with 80% power (two-sided α -level of 0.05) for detecting an increase in the angiographic restenosis rate of 33% (from 36% as assumed in the group of patients with the 34CC genotype to 48% in the group of patients with the 34GG or 34CG genotype [G allele carriers]) and accommodating for a missing follow-up angiography rate of up to 25%.

The 34C/G and 1431C/T polymorphisms were analysed using the TaqMan technique (Applied Biosystems, Darmstadt, Germany). PPAR γ genotypes were distributed as 75.9% 34CC, 22.9% 34CG, 1.2% 34GG and 75.3% 1431CC, 23.2% 1431CT, 1.5% 1431TT. For comparisons with the carriers of the abundant 34CC and 1431CC genotypes, the patients with the rare 34GG and 1431TT genotypes were combined with the patients who carried the 34CG and 1431CT genotypes respectively.

The rates of major adverse clinical events due to thrombosis (death from any cause, non-fatal acute myocardial infarction and urgent target vessel revascularisation) were not significantly different between the genotype groups of the 34C/G and 1431C/T polymorphisms ($p \geq 0.35$) during the early 30-day period after stenting.

Follow-up angiography of coronary arteries was performed in 695 patients (74.3%). The proportions of patients undergoing 6-month angiography were not substantially different between the genotype groups of the 34C/G polymorphism ($p=0.83$) and the 1431C/T polymorphism ($p=0.52$). Table 1 shows the quantitative angiographic results of the genotype groups. Angiographic restenosis rates were not significantly different between the patients with the 34CC genotype and the carriers of the 34G allele, or between the patients with the 1431CC genotype and the carriers of the 1431T allele ($p \geq 0.73$). After adjustment for baseline and lesion-related variables, multivariate analysis did not reveal a significant independent association of the 34C/G polymorphism ($p=0.68$) or

Table 1. Results of 6-month follow-up angiography (n=695)

	34CC (n=529)	34CG + 34GG (n=166)	<i>p</i> value	1431CC (n=527)	1431CT + 1431TT (n=168)	<i>p</i> value
Minimal lumen diameter (mm)	1.61±0.92	1.62±0.91	0.86	1.61±0.92	1.60±0.91	0.90
Diameter stenosis (%)	45.4±28.2	45.4±28.1	0.99	45.5±28.1	45.0±28.4	0.83
Late lumen loss (mm)	1.24±0.80	1.28±0.86	0.56	1.25±0.82	1.23±0.82	0.74
Loss index	0.44±0.29	0.43±0.29	0.78	0.44±0.29	0.43±0.29	0.65
Angiographic restenosis	193 (36.5)	63 (38.0)	0.73	194 (36.8)	62 (36.9)	0.98

Data are presented as the mean value (±SD) or the number (%) of patients

the 1431C/T polymorphism ($p=0.82$) with angiographic restenosis. The adjusted odds ratios were 1.08 (95% CI: 0.74–1.59) for the 34C/G polymorphism and 0.96 (95% CI: 0.65–1.40) for the 1431C/T polymorphism. In addition, the incidence of angiographic restenosis was not dependent on the treatment of the patients with insulin or oral antidiabetic agents (34CC vs 34G, $p=0.28$; 1431CC vs 1431T, $p=0.45$), and we did not find substantial differences in angiographic restenosis rates between the female and male individuals (34CC vs 34G, $p=0.17$; 1431CC vs 1431T, $p=0.59$). Continuous measures of angiographic restenosis, diameter stenosis, late lumen loss and loss index were not distributed differently between the patient groups ($p\geq 0.56$; Table 1). Within the entire study population of 935 patients, the need for target vessel revascularisation due to symptoms or signs of ischaemia in the presence of angiographic restenosis at the stented site (clinical restenosis) was not significantly different between the groups over 1 year: 18.3% in the patients with the 34CC genotype and 18.2% in the carriers of the 34G allele ($p=0.98$); 18.8% in the patients with the 1431CC genotype and 16.9% in the carriers of the 1431T allele ($p=0.52$).

Complete 1-year clinical follow-up data were available for all patients, irrespective of the presence or absence of follow-up angiography. The combined incidence of all-cause death or non-fatal myocardial infarction was 9.9% among the patients with the 34CC genotype and 8.9% among the 34G allele carriers ($p=0.67$). This endpoint was reached in 9.4% of the patients with the 1431CC genotype and in 10.4% of the 1431T allele carriers ($p=0.65$).

In summary, the results of the present study indicate that the 34C/G and 1431C/T polymorphisms of the PPAR γ gene are not associated with the incidence of restenosis and adverse clinical events at 30 days or 1 year after coronary artery stenting in patients with diabetes mellitus.

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