Objective: Drug-eluting stents (DES) have reduced restenosis rates compared with bare-metal stents. P27 and P53 play important roles in the signal transduction leading to neointimal growth inhibition and induction of apoptosis of smooth muscle cells due to rapamycin and paclitaxel. We hypothesized that genetic variants of P27 and P53 influence the development of restenosis and the clinical outcome of patients receiving DES. Methods: Polymorphisms in the genes encoding for P27 and P53 were tested for their association with restenosis and major adverse cardiac events. P27 C-79T and P53 G72C polymorphism genotypes were determined in a series of 433 consecutive patients receiving DES. Follow-up angiography after 6 months was performed in 87% of the patients. Genotyping was performed with PCR-based methods. Results: For patients with the respective P27 C-79T and P53 G72C genotypes, the angiographic restenosis rates were between 5.0 and 22.0%, and the clinical restenosis rates were between 0.0 and 16.3%, without significant differences for the studied genotypes (p > 0.19). There was no association of the studied genotypes with the 1-year incidences of death and myocardial infarction. Conclusion: This study could not demonstrate a clinically relevant role of P27 and P53 polymorphisms in the processes leading to in-stent restenosis.