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A Randomized Comparison of Sirolimus- Versus Paclitaxel-Eluting Stent Implantation in Patients With Diabetes Mellitus

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Objectives The aim of this study was to compare the effectiveness of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in patients with diabetes mellitus (DM).

Background Drug-eluting stent implantation significantly improved the angiographic and clinical outcomes compared with bare-metal stent implantation in diabetic patients. However, comparison of SES with PES in diabetic patients has not been sufficiently evaluated.

Methods This prospective, multicenter, randomized study compared SES (n = 200) and PES implantation (n = 200) for diabetic patients (n = 400). The primary end point was in-segment restenosis at 6 months according to intention-to-treat principle.

Results The 2 groups had similar baseline clinical and angiographic characteristics. Six-month in-stent (3.4% vs. 18.2%, $p < 0.001$) and in-segment restenosis (4.0% vs. 20.8%, $p < 0.001$) and 9-month target lesion revascularization (2.0% vs. 7.5%, $p = 0.017$) were significantly lower in the SES versus the PES group. The incidence of death (0% in SES vs. 0.5% in PES, $p = 0.999$) or myocardial infarction (0.5% in SES vs. 0.5% in PES, $p = 0.999$) at 9-month follow-up was not statistically different between the 2 groups. Major adverse cardiac events including death, myocardial infarction, and target lesion revascularization at 9 months (2.0% vs. 8.0%, $p = 0.010$) were lower in the SES versus the PES group.

Conclusions Sirolimus-eluting stent implantation is superior in reducing angiographic restenosis and improving 9-month clinical outcomes in patients with DM and coronary artery disease compared with PES implantation. (J Am Coll Cardiol 2008;52:727–33) © 2008 by the American College of Cardiology Foundation

Diabetic patients often present unfavorable coronary anatomy with small and diffusely diseased vessels (1) and exhibit exaggerated neointimal hyperplasia after bare-metal stent (BMS) implantation compared with nondiabetic subjects (2). Although drug-eluting stent (DES) implantation significantly reduced the neointimal hyperplasia and angiographic restenosis compared with BMS in diabetic patients (3), presence of diabetes mellitus (DM) has been still associated with an increased risk of restenosis and unfavorable clinical outcomes in the era of DES (4,5). Recently, the relative efficacies of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in patients with DM have been evaluated in randomized and registry studies (6–10). Although some studies found SES to have greater efficacy than PES in diabetic patients (9,10), controversy remains (6–8). Therefore, to compare the effectiveness of 2 DES

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Abbreviations and Acronyms

AMI = acute myocardial infarction
BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
DM = diabetes mellitus
IQR = interquartile range
MACE = major adverse cardiac events
MI = myocardial infarction
MLD = minimal lumen diameter
PES = paclitaxel-eluting stent(s)
QCA = quantitative coronary angiography
RR = relative risk
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

(SES and PES) in patients with DM, we performed a randomized, multicenter, prospective study comparing SES and PES in diabetic patients (DES-DIABETES [Drug-Eluting Stent in patients with DIABETES mellitus] trial).

Methods

Patient selection. This prospective randomized study included 400 patients ≥18 years of age with angina pectoris and/or a positive stress test and a native coronary lesion. The study involved 5 cardiac centers in Korea between May 2005 and March 2006. Patients were considered eligible if they had DM, presented with angina pectoris, or had a positive stress test and had clinically significant angiographic stenosis in a native coronary vessel with a diameter stenosis ≥50% and visual reference diameter ≥2.5 mm. Patients were excluded if they had a contraindication to aspirin, clopidogrel, or cilostazol; left main disease (diameter stenosis ≥50% by visual estimate); graft vessel disease; left ventricular ejection fraction <30%; recent history of hematologic disease or leukocyte count <3,000/mm^3 and/or platelet count <100,000/mm^3; hepatic dysfunction with asparatate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 times the upper normal reference limit; history of renal dysfunction or serum creatinine level ≥2.0 mg/dl; serious noncardiac comorbid disease with a life expectancy <1 year; planned bifurcation stenting in the side branch; primary angioplasty for acute myocardial infarction (AMI) within 24 h; or inability to follow the protocol. In patients with multiple lesions fulfilling the inclusion and exclusion criteria, the first stented lesion was considered as target lesion. The institutional review board at each participating center approved the protocol. All patients provided written informed consent.

Randomization and procedures. Once the guidewire had crossed the target lesion, patients were randomly assigned in a 1:1 ratio to SES or PES implantation. After DES randomization, patients were randomly allocated in a 1:1 ratio to the triple antiplatelet group (aspirin, clopidogrel, and cilostazol; triple group; n = 200) or the dual antiplatelet therapy group (aspirin and clopidogrel; standard group; n = 200) (antiplatelet arm) on the basis of a 2 × 2 factorial design with a computer-generated randomization sequence. Random assignments were stratified according to participation sites and blocked with block size of 4 or 6 and were distributed in sealed envelopes to each participating center. The block size was concealed. From at least 24 h before the procedure and thereafter, all patients received aspirin (200 mg daily) and clopidogrel (loading dose of 300 mg, followed by 75 mg daily for at least 6 months). Patients in the triple group received a loading dose of 200 mg cilostazol immediately after the procedure and 100 mg twice/day for 6 months.

Coronary stenting was performed with the standard technique. The decision of pre-dilation or direct stenting was made by the operator. The use of intravenous glycoprotein IIb/IIIa inhibitors was at the operator's discretion. A 12-lead electrocardiogram was obtained after the procedure and before discharge. Serum levels of creatine kinase-myocardial band isoenzyme were assessed 8, 12, and 24 h after the procedure and thereafter if considered necessary.

Study end point and definitions. The primary end point of this trial was in-segment restenosis on 6-month follow-up study (defined as in-segment stenosis of at least 50%). The secondary end points included 6-month angiographic outcomes such as in-segment late loss and the rate of in-stent restenosis at 6 months (defined as in-stent stenosis of at least 50%), stent thrombosis, target vessel revascularization (TVR), and major adverse cardiac events (MACE) including death, myocardial infarction (MI), and target lesion revascularization (TLR).

The diagnosis of DM was considered confirmed in all patients receiving active treatment with an oral hypoglycemic agent or insulin; for patients with a diagnosis of diabetes who were on a dietary therapy alone, enrollment in the trial required the documentation of an abnormal blood glucose level after an overnight fast. Angiographic success was defined as in-segment final diameter stenosis <30% by quantitative coronary angiography (QCA). A Q-wave MI was defined by the post-procedural presence of new Q waves of >0.04 s in 2 contiguous leads. Non–Q-wave MI was defined as a creatine kinase-myocardial band fraction >3 times the upper limit of normal. Target lesion revascularization was considered clinically driven if prompted by symptoms consistent with myocardial ischemia, if preceded by an abnormal stress test result consistent with myocardial ischemia, if there were other electrocardiographic changes consistent with myocardial ischemia, or if the lesion diameter stenosis was more than 70% at follow-up (11). Stent thrombosis was defined as any of the following after the procedure: angiographic documentation of stent occlusion with or without the presence of thrombus associated with an acute ischemic event, unexplained sudden death, or MI not clearly attributable to another coronary lesion (12,13).

Follow-up. Repeat coronary angiography was mandatory at 6 months after stenting or earlier if indicated by clinical symptoms or evidence of myocardial ischemia. Clinical follow-up visits were scheduled at 30, 90, 180, and 270 days. At every visit, physical examination, electrocardiogram, cardiac events, and angina recurrence were monitored. At each participating center, patient data were recorded prospectively on standard case report forms and gathered in the central data