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Clinical Efficacy of Drug-Eluting Stents in Diabetic Patients

A Meta-Analysis

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Objectives The purpose of this study was to compare estimates for revascularization and major adverse cardiac events (MACE) (death, myocardial infarction, repeat revascularization) in diabetic patients treated with paclitaxel- and sirolimus-eluting stents (PES and SES).

Background Outcomes in diabetic patients treated with PES and SES have not been adequately evaluated.

Methods We searched MEDLINE/EMBASE from January 2002 to February 2007 and identified abstracts/presentations from this period at major cardiology conferences. Randomized controlled trials (RCTs) and registries were included if data for diabetic patients treated with PES or SES were available. Point estimates with 95% confidence intervals (CIs) were computed as summary statistics.

Results In RCTs (13 trials; n = 2,422) similar point estimates for target lesion revascularization (TLR) (PES: 8.6%, 95% CI 6.5% to 11.3%; SES: 7.6%, 95% CI 5.8% to 9.9%) and MACE (PES: 15.4%, 95% CI 12.4% to 19.1%; SES: 12.9%, 95% CI 8.5% to 19.2%) were observed. In head-to-head trials (4 RCTs), no difference in the likelihood of TLR (PES vs. SES) was observed (odds ratio [OR] 1.37, 95% CI 0.64 to 2.9, p = 0.42). In registries (16 registries; n = 10,156), point estimates for target vessel revascularization (TVR) (PES: 5.8%, 95% CI 3.9% to 8.5%; SES: 7.2%, 95% CI 4.6% to 11.2%) and MACE (PES: 10.1%, 95% CI 7.3% to 13.8%; SES: 11.9%, 95% CI 8.6% to 16.4%) were also similar. In registries reporting outcomes with both stents (8 registries for TVR and 7 registries for MACE), the likelihood of TVR (PES vs. SES) (OR 0.77, 95% CI 0.54 to 1.10, p = 0.15) and MACE (OR 0.83, 95% CI 0.68 to 1.01, p = 0.056) were nonsignificantly lower with PES.

Conclusions This analysis of over 11,000 diabetic patients treated with drug-eluting stents demonstrates single-digit revascularization rates. Furthermore, revascularization and MACE estimates are similar with both PES and SES. (J Am Coll Cardiol 2008;51:2385–95) © 2008 by the American College of Cardiology Foundation

Epidemiological data have firmly established a relationship between coronary heart disease and diabetes mellitus (1). Although the precise mechanism behind this relationship remains uncertain, hyperglycemia, abnormal lipid metabolism, and insulin resistance, coupled with frequently occurring hypertension, result in acceleration of the atherosclerotic process (2). Coronary artery disease is currently responsible for three-quarters of diabetes-related deaths (3), and as the prevalence of diabetes increases, the number of diabetic patients requiring revascularization for advanced coronary artery disease will escalate.

Outcomes with either percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery are poorer for diabetic than nondiabetic patients (4). Percutaneous coronary intervention with bare-metal stents (BMS) was limited in diabetic patients, owing to higher restenosis rates (5). The paclitaxel-eluting stent (PES) Taxus (Boston Scientific, Natick, Massachusetts) and the sirolimus-eluting stent (SES) Cypher (Johnson & Johnson, Miami Lakes, Florida) are both effective in reducing the need for repeat revascularization compared with BMS (6–12), and this has led to PCI being used more frequently in diabetic patients (13,14). However, the

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
MACE = major adverse cardiac event
OR = odds ratio
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RCT = randomized controlled trial
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

use of DES in diabetic patients is considered off label by the Food and Drug Administration, because adequate numbers of diabetic patients have not been evaluated in clinical trials (15,16). Furthermore, data regarding the relative efficacy of the 2 stents in diabetic patients are less clear. There has only been 1 randomized controlled trial (RCT) comparing the 2 stents exclusively in diabetic patients, and this study included only 125 patients in each arm and also did not have a clinical end point (17). Because late luminal loss is greater with the PES than the SES (6,12), it could be hypothesized that diabetic patients, who have a higher proclivity to restenosis, would have worse clinical outcomes with the PES. However, an attenuation of the antimigratory effect of sirolimus described in the presence of hyperglycemia (18) could lead to lower efficacy of SES in diabetic patients. In addition, the variability in stent platforms, polymer technology, and delivery systems could also lead to differences in clinical outcomes between the 2 stents.

The evaluation of diabetic patients treated with PES and SES in multiple RCTs and registries provides an opportunity to determine clinical outcomes of DES in diabetic patients and to compare the relative efficacy and safety of these 2 DES. With suggested guidelines (19), this meta-analysis was performed to estimate target lesion revascularization (TLR), major adverse cardiac events (MACE), and stent thrombosis, for diabetic patients receiving either PES or SES as part of an RCT and to compare the efficacy of the 2 DES from head-to-head RCTs. With registry data, we also estimated target vessel revascularization (TVR) and MACE for diabetic patients receiving either DES. Comparison of the 2 DES from registries that reported outcomes with both stents in similar populations was also separately performed. Because angiographic measures, such as binary restenosis and late loss, are debatable end points for clinical utility in individual patients and are not available for most registries, we specifically chose not to include them in this analysis.

Methods

Identification and selection of studies. A search was conducted of the English language published reports in MEDLINE and EMBASE from January 2002 to February 2007. Abstracts and presentations from this time period at major international cardiology conferences (American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and Paris Course on Revascularization) were also reviewed. The search terms "drug," "eluting," and "stent" were combined with the terms "registry" or "registries" and then "clinical" and "trial" or "trials" as 2 distinct published report searches. The RCTs and registries were included in the analysis if data for diabetic patients treated with a PES or SES were available for at least 1 of the clinical end points (TLR or MACE for RCTs; TVR or MACE for registries) being assessed and were not duplicative. Target lesion revascularization was defined as any procedure (PCI or coronary artery bypass graft surgery) performed to revascularize the index lesion, whereas TVR was defined as any procedure to revascularize the index vessel. Although the definition of MACE varied slightly in the various studies, it usually consisted of cardiac death, myocardial infarction, and repeat revascularization.

RCTs. All studies and abstracts/presentations were identified and reviewed by at least 2 of the authors. The RCTs

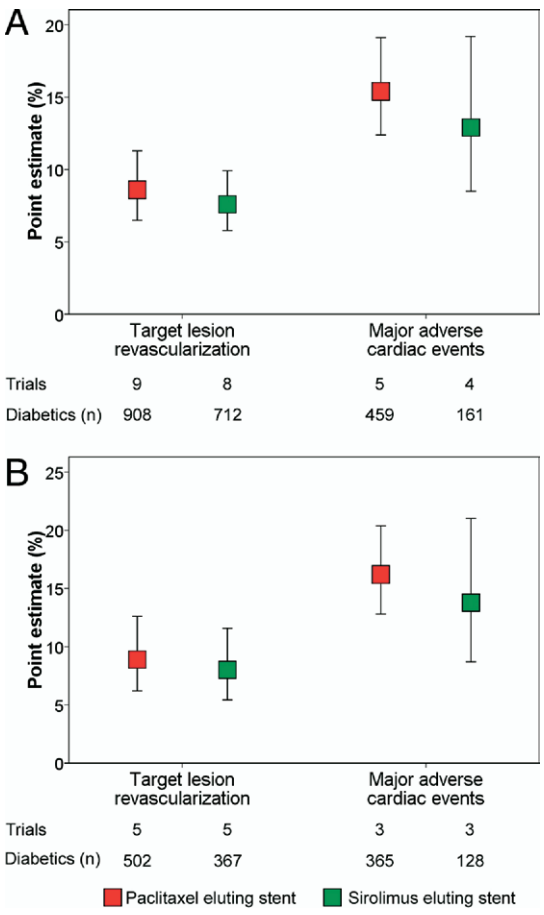

Figure 1 Clinical Event Rates for Diabetic Patients Treated With DES in RCTs

Point estimates for target lesion revascularization and major adverse cardiac events for diabetic patients treated with drug-eluting stents (DES) in **(A)** all randomized controlled trials (RCTs) and **(B)** RCTs with Silber score >5. **Bars** indicate 95% confidence intervals.