

Eighteen-Month Clinical Safety and Efficacy Outcomes of Sirolimus-, Paclitaxel- and Zotarolimus-drug Eluting Stents in Diabetic Patients Undergoing Percutaneous Coronary Intervention for Complex Coronary Artery Stenosis

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Abstract

Introduction: This was a single centre registry study on clinical efficacy and safety of drug-eluting stent (DES) in diabetic patients undergoing percutaneous coronary intervention (PCI) for complex coronary lesions. **Materials and Methods:** A total of 288 diabetic patients who underwent elective PCI between September 2003 and June 2006 in our centre were enrolled and followed-up for 18 months. Among them, 79 (27.4%) patients received sirolimus-eluting stent (SES), 138 (47.9%) paclitaxel-eluting stent (PES) and 71 (24.7%) zotarolimus-eluting stent (ZES). The endpoints were major adverse cardiac events (MACE) and stent thrombosis rates. **Results:** Baseline demographics were comparable among the 3 DES groups (median age was 60 years; 69% men). Complex lesions (defined as ACC/AHA type C stenosis) accounted for 55.6% of the total lesions: SES (50.6%), PES (65.2%) and ZES (43.7%), $P = 0.005$. At 18 months follow-up, the composite endpoint of MACE was found in 12.7% in SES group, 8.7% in the PES group, 12.7% in ZES group and ($P = 0.55$). Stent thrombosis (ST) occurred in 1 patient (1.3%) in the SES group, 2 patients (1.4%) in PES group and 1 patient (1.4%) in ZES group, respectively ($P = 1.00$). **Conclusion:** The use of DES for elective PCI in diabetic patients was associated with favourable intermediate-term clinical outcomes with no significant differences in efficacy among the 3 groups. Stent thrombosis had low event occurrence rate.

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Key words: Drug-eluting coronary stents, Diabetes mellitus, Stent thrombosis

Introduction

Patients with diabetes mellitus (DM) have higher incidence of cardiovascular morbidity and mortality compared with non-diabetic patients.¹ The underlying mechanism is due to the more diffuse and accelerated form of atherosclerosis and endothelial dysfunction which lead to diffuse coronary lesions, small vessel disease, multi-vessel involvement, larger plaque burden as well as higher incidence of left main and ostial lesions.²

Coronary interventional trials in diabetic patients using bare metal stents (BMS) showed high restenosis rates and major adverse cardiac events (MACE) which is a composite endpoint of death, non-fatal myocardial infarction and target vessel revascularisation.^{3,4} To date, drug eluting stents (DES) namely sirolimus-, paclitaxel- and zotarolimus-eluting stents (SES, PES and ZES) have shown to be more

effective in reducing the restenosis rate and hence target vessel revascularisation (TVR) in diabetic patients when compared with BMS at 6 months and 1 year.^{5,6} It is interesting to look at intermediate-term clinical endpoints of MACE and stent thrombosis among the different types of DES in the high-risk diabetic cohort.^{7,8} The aim of this study was to present the 18-month clinical experience on the use of 3 DES in diabetic patients with complex coronary lesions.

Materials and Methods

Study Design and Patient Population

A total of 288 diabetic patients who underwent elective PCI between September 2003 and June 2006 in the University Heart Centre were enrolled in the study. The stents studied were SES (Cypher®, Cordis, Johnson & Johnson Company, New Jersey, USA), PES (Taxus Express

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and Liberte®, Boston Corporations, Massachusetts, USA) and ZES (Endeavour®, Medtronic, Minneapolis, USA).

Procedures and Post-intervention Medications

Angiographic success was defined as a residual stenosis $\leq 30\%$ by visual analysis in the presence of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. Quantitative coronary angiography (QCA) was performed in the core lab by an interventional cardiologist performing the percutaneous coronary intervention (PCI). Patients were pretreated with loading doses of aspirin (300 mg) and clopidogrel (300 mg) followed by 100 mg of aspirin long-term and 75 mg of clopidogrel for 12 months accordingly to current guidelines.

Endpoint Definitions and Clinical Follow-up

The 18 months clinical and angiographic data were used for the primary endpoint analysis. Coronary revascularisation procedures, complication during hospitalisation and mortality rates were prospectively collected during follow-up by cardiac research nurses and these data were entered into a predefined cardiovascular database.

The primary endpoint of the study was the occurrence of MACE. Post-procedural myocardial infarction (MI) was defined by an increase in creatinine kinase-MB (CKMB) greater than 3 times the normal upper limit. TVR was defined as re-intervention of a lesion in the same coronary artery. Sub-acute angiographic stent thrombosis was defined as an angiographically documented coronary occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) in the first 30 days post-PCI. Late-stent thrombosis was defined as angiographically defined thrombosis occurring 1 month after PCI accompanied by acute symptoms.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD. Categorical variables are expressed as counts and percentages. Comparisons among the 3 groups were performed by the F-test from an analysis of variance for continuous variables and Pearson's chi-square test for categorical variables. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method and the log-rank test was used to evaluate differences between groups. In all cases, $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 14.0 for Windows (SPSS Inc Chicago).

Results

Baseline and Procedural Characteristics

Among the 288 diabetic patients treated with DES: 79 (27.4%) received SES, 138 (47.9%) received PES and

Table 1. Baseline Clinical Characteristics

	SES (n = 79)	PES (n = 138)	ZES (n = 71)	P
Age (years $\pm$ SD)	60.0 $\pm$ 9.9	58.6 $\pm$ 10.0	60.7 $\pm$ 13.4	0.60
Male, n (%)	54 (68.4)	97 (70.1)	48 (67.7)	0.72
Hypertension, n (%)	60 (75.9)	105 (76.1)	53 (74.6)	0.97
Hyperlipidaemia, n (%)	65 (82.3)	106 (76.8)	54 (76.1)	0.71
Smoker, n (%)	21 (26.6)	36 (26.4)	19 (26.9)	0.91
Previous PCI, n (%)	17 (21.5)	17 (12.3)	12 (16.9)	0.20
Previous CABG, n (%)	3 (3.8)	10 (7.2)	6 (8.5)	0.47
LVEF (%)	53.2 $\pm$ 10.8	52.5 $\pm$ 10.2	53.6 $\pm$ 10.3	0.50

CABG: coronary artery bypass grafting; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; SD: standard deviation; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

Table 2. Angiographic and Procedural Characteristics

	SES (n = 79)	PES (n = 138)	ZES (n = 71)	P
Treated coronary vessel				0.63
LAD, n (%)	44 (55.7)	94 (68.1)	49 (69.0)	
LCX, n (%)	13 (16.5)	12 (8.7)	7 (9.9)	
RCA, n (%)	18 (22.8)	23 (16.7)	12 (16.9)	
LM, n (%)	1 (1.3)	1 (0.7)	1 (1.4)	
Bypass graft, n (%)	3 (3.8)	8 (5.8)	3 (4.2)	
Lesion type				0.005
Type A, n (%)	3 (3.8)	0 (0)	3 (4.2)	
Type B1, n (%)	12 (15.2)	9 (6.5)	12 (16.9)	
Type B2, n (%)	24 (30.4)	39 (28.3)	25 (35.2)	
Type C, n (%)	40 (50.6)	90 (65.2)	31 (43.7)	
Stent number	1.6	1.8	1.23	0.18
Stent length (mm)	25.2	23.7	21.4	0.26
Mean reference artery diameter (mm)	2.62 $\pm$ 0.88	2.79 $\pm$ 0.84	2.78 $\pm$ 0.88	0.09
MLD (mm)				
Before	0.39 $\pm$ 0.31	0.44 $\pm$ 0.33	0.46 $\pm$ 0.33	0.11
After	2.74 $\pm$ 0.72	2.88 $\pm$ 0.63	2.73 $\pm$ 0.95	0.04
DS (%)				
Before	84.21 $\pm$ 12.75	84.06 $\pm$ 11.84	82.07 $\pm$ 13.58	0.20
After	6.53 $\pm$ 3.76	6.26 $\pm$ 4.01	4.95 $\pm$ 4.42	<0.001

DS: diameter stenosis; LAD: left anterior descending; LCX: left circumflex; LM: left main; MLD: minimal lumen diameter; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; RCA: right coronary artery; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent
Intracoronary GTN was administered before the final angiographic shot for Post-PCI QCA analysis.

71 (24.7%) received ZES. Baseline, angiographic and procedural characteristics are shown in Tables 1 and 2. Baseline demographics were comparable among the 3 groups (mean age was 60 years; 69% men). Complex coronary lesions (defined as ACC/AHA Type C stenosis) accounted for 55.6% of the total treated lesions. There were slightly more type C lesions treated with PES (65.2%) than SES (50.6%) and ZES (43.7%), $P = 0.005$.

18-month Follow-up

At 18-month follow-up, the cumulative incidence of mortality among the 3 groups were: 2.5% (SES) vs 0.7% (PES) vs 4.2% (ZES), $P = 0.134$ (Table 3). There was 1 death in the SES group, 1 death in the PES group and 3 deaths in the ZES group that occurred during the initial 6 months of follow-up. There was an additional death in the SES group at 18 months of follow-up. The cumulative incidence of MI was higher by absolute percentage value in the SES group (8.9%) when compared to the PES (5.1%) and ZES groups (5.6%). However, this was not statistically significant ($P = 0.54$). The cumulative incidence rates of TVR in the 3 groups were comparable: 6.3% (SES) vs 5.8% (PES) vs 5.6% (ZES), $P = 1.00$ (Table 3). The composite endpoint of MACE was found in 12.7% of the SES group which was comparable with the ZES group (12.7%). The MACE rate in the PES group (8.7%) was lower when compared with the other 2 groups but this was not statistically significant ($P = 0.55$) (Table 3). There was no incidence of acute ST (defined as angiographic stent thrombosis within 24-hour post-PCI) in all 3 groups. However, subacute ST occurred in 1 (0.7%) patient in the PES group at Day 9 and 1 (1.4%) patient in the ZES group at Day 17. There was no subacute ST in the SES group. The incidence of late ST was low in the 3 groups with 1 (1.3%) patient in the SES group at 4 months and 1 (0.7%) patient in the PES group at 13 months. There was no late ST in the ZES group. All 4 patients who developed ST presented with acute MI. Three patients were still on dual-antiplatelets therapy at the time of the

event. By using the Academic Research Consortium (ARC) definition, the stent thrombosis rates in the 3 groups were SES (3.8%), PES (2.1%) and ZES (5.6%), respectively.

Discussion

In our registry of diabetic patients who received the 3 different DES during PCI, there were no significant differences in the risk of death, MI, TVR and stent thrombosis at 18 months of clinical follow-up. These DES appeared to have comparable and favourable clinical efficacy and safety in the high-risk diabetic patient cohort.

DES has been shown to be superior to BMS in terms of clinical and angiographic restenosis in patients with DM from 1 to 5 years of follow-up.^{9,10} Our registry findings with these commonly used DES are similar to that in other registry findings. In the ISAR-Diabetes registry study showing intermediate-term follow-up on diabetes patients, the TVR after SES implantation was 6.4% and there were no clinical differences between SES and PES in the clinical endpoints at the end of follow-up.¹¹ These data are comparable to our study results. The study on ZES also showed similar rates of TVR and MACE.¹² Clinical endpoints of different DES were shown to be comparable among SES, PES and ZES in the SCARR registry in the subgroup of diabetic patients.¹³ Our registry concerning these DES performances showed similar results to these prior registries and trials at intermediate-term.

The incidence of stent thrombosis in our DES groups was low and comparable to published data.¹⁴ Studies reporting the incidence of ST following PCI with DES in the general population reported ST rates of 1.0% to 1.6% and identified DM as an important independent predictor of its occurrence.¹⁵ Our results did not show an excessive incidence of ST in our diabetic population. Among our cases of ST, 1 patient on PES had stopped clopidogrel at the twelfth month and ST developed 1 month later. This case of very late ST incidence may lead us to reconsider a longer duration of dual antiplatelet therapy. By using the ARC criteria defining stent thrombosis, the incidence rate in our cohort is again comparable to established data.¹⁴

In our study, high-risk AHA/ACC type C coronary lesions comprised approximately 55% of the study population. The clinical TVR rates remained as single digit. This supports a favourable clinical outcome at intermediate-term of using DES in diabetic patients.

Limitations

The major limitation of our study was the inherent problems of a single centre registry study. There can be potential confounding factors although baseline characteristics of the 3 DES groups were fairly similar. It was noted that even though the PES group had higher

Table 3. 18-month MACE Among 3 Groups

	SES (n = 79)	PES (n = 138)	ZES (n = 71)	P
MACE	10 (12.7%)	12 (8.7%)	9 (12.7%)	0.55
Death	2 (2.5%)	1 (0.7%)	3 (4.2%)	0.13
MI	7 (8.9%)	7 (5.1%)	4 (5.6%)	0.54
TVR	5 (6.3%)	8 (5.8%)	4 (5.6%)	1.00
Stent thrombosis	1 (1.3%)	2 (1.4%)	1 (1.4%)	1.00
Stent thrombosis ARC definition	3 (3.8%)	3 (2.1%)	4 (5.6%)	0.43

MACE: major adverse cardiac events; MI: myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TVR: target vessel revascularisation; ZES: zotarolimus-eluting stent

AHA/ACC type C lesions (65.2% PES vs 50.6% SES vs 43.7% ZES), the overall clinical efficacy and hard endpoints were comparable to the other groups. These may be partly attributable to a comparatively larger minimal lumen diameter (MLD) post-PCI in the PES group (2.88 mm in PES group vs 2.74 mm in SES group vs 2.73 mm in ZES group, $P = 0.04$).

Nevertheless, this report focuses on an intermediate-term clinical follow-up in the use of 3 DES in a high-risk diabetic population. It provides medium-term follow-up findings of DES which showed comparable efficacy and safety.

Conclusion

In our registry, the use of DES in diabetic patients with complex coronary lesions was associated with favourable intermediate-term clinical outcomes with single digit clinical TVR. There were comparable MACE rates among the 3 DES groups. Stent thrombosis remained a low event occurrence in all 3 DES groups.

Conflict of interest: none for all authors

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