Impact of Diabetes Mellitus on Angiographic and Clinical Outcomes in the Drug-Eluting Stents Era

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The effect of diabetes mellitus (DM) on angiographic restenosis and clinical outcomes after implantation of drug-eluting stents (DESs) has not been investigated in real-world practice. This study consisted of 226 patients who had DM and 560 patients who did not who underwent DES implantation between February 2003 and December 2003. We retrospectively compared the incidence of 6-month angiographic restenosis and 9-month major adverse cardiac events (MACEs), defined as cardiac death, myocardial infarction, and target lesion revascularization, between patients with and without DM. The 6-month angiographic restenotic rate (10.1% vs 8.2%, p = 0.41) and late loss (0.41 ± 0.63 vs 0.36 ± 0.65, p = 0.31) were similar between patients with and without DM. In addition, incidences of MACEs (4.9% vs 4.8%, p = 1.00) and target lesion revascularization (4.4% vs 4.1%, p = 0.84) were similar. Patients who had insulin-dependent DM manifested higher prevalences of restenosis (25.0% vs 8.5%, p = 0.04) and MACEs (17.2% vs 3.1%, p = 0.01) compared with patients who had non–insulin-dependent DM. In conclusion, in this study of real-world patients who underwent DES implantation, patients who had DM had restenotic rates and clinical outcomes that were similar to those in patients who did not have DM. **(Am J Cardiol 2005;96: 1389–1392)**

This study evaluated and compared the effect of drug-eluting stents (DESs) on angiographic and clinical outcomes of patients who had diabetes mellitus (DM) and patients who did not and who underwent percutaneous coronary intervention in real-world practice.

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This study consisted of 786 consecutive patients who underwent DES implantation between February 2003 and December 2003; 226 patients (299 lesions) had DM and 560 (705 lesions) did not. Patients who had ST-segment elevation myocardial infarction and were eligible for primary percutaneous coronary intervention were excluded. Sirolimus-eluting stents (Cypher stent, Cordis Corp., Johnson & Johnson Company, Warren, New Jersey) and paclitaxel-eluting stents (TAXUS stent, Boston Scientific Corp., Natick, Massachusetts) were implanted. Patients who were considered to have DM were those who used oral hypoglycemic agents or required insulin for adequate glucose control at the time of percutaneous coronary intervention. The study protocol was approved by the hospital's institutional review board. Lesions were treated according to standard interventional techniques. Selection of the type of DES and use of glycoprotein IIb/IIIa antagonists were left to the discretion of the operators. Heparin was given to all patients during the procedure to maintain an activated clotting time of ≥250 seconds. The postprocedural antiplatelet regimen consisted of lifelong aspirin (200 mg/day) and clopidogrel (300 mg loading dose, 75 mg/day for ≥6 months). Coronary angiographic results were analyzed with an off-line quantitative coronary angiographic system (ANCOR V2.0, Siemens, Solna, Sweden) by 2 experienced angiographers who were unaware of the patients' DM status. Quantitative coronary angiographic parameters were measured in an analysis segment within the stent or in the 5-mm segments proximal or distal to the stent. Binary restenosis at follow-up was defined as a diameter stenosis ≥50%. Acute gain was defined as the difference in minimal luminal diameter before and after the procedure. Late loss was calculated as the difference in minimal luminal diameter immediately after the procedure and at 6 months. Late loss index was calculated as late loss divided by acute gain. Clinical outcomes at 9 months were obtained by outpatient visits to a clinic or telephone interviews. Patients were evaluated for the occurrence of major adverse cardiac events (MACEs): death by cardiac cause, nonfatal myocardial infarction, and target lesion revascularization at 9 months. Reinfarc-

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Table 1
Baseline clinical and procedural characteristics

Variables	DM		p Value
	Yes (n = 226)	No (n = 560)	
Age (yrs)	61.3 ± 9.8	60.9 ± 10.4	0.74
Men	160 (71%)	408 (73%)	0.56
Hypertension	129 (57%)	281 (50%)	0.11
Hypercholesterolemia*	45 (20%)	134 (24%)	0.29
Currently smoking	56 (25%)	175 (31%)	0.08
Previous myocardial infarction	52 (23%)	114 (20%)	0.41
Previous percutaneous intervention	60 (27%)	130 (23%)	0.36
Previous coronary bypass surgery	9 (4%)	19 (3%)	0.69
Left ventricle ejection fraction	57 ± 10	59 ± 10	0.21
Multivessel coronary disease	154 (68%)	327 (58%)	0.01
Stent length (mm)	32.5 ± 19.1	29.2 ± 15.6	<0.01
Use of glycoprotein IIb/IIIa inhibitor	18 (8%)	58 (10%)	0.35
Insulin-dependent DM	30 (13%)	—	—

* Total cholesterol level >200 mg/dl.

Table 2
Baseline coronary angiographic characteristics

Variables	DM		p Value
	Yes (n = 299)	No (n = 705)	
Lesion location			0.62
Left main coronary artery	28 (9%)	69 (10%)	
Left anterior descending coronary artery	141 (47%)	334 (47%)	
Left circumflex coronary artery	51 (17%)	97 (14%)	
Right coronary artery	77 (26%)	195 (28%)	
Graft	2 (1%)	10 (1%)	
Ostial lesion	13 (4%)	39 (6%)	0.44
Bifurcation lesion	56 (19%)	149 (21%)	0.39
Chronic total occlusion lesion	12 (4%)	42 (6%)	0.21
Lesion classification*			0.18
Type A	10 (3%)	40 (6%)	
Type B1	67 (22%)	188 (27%)	
Type B2	33 (11%)	90 (13%)	
Type C	189 (63%)	387 (55%)	
Use of sirolimus-eluting stents	208 (70%)	490 (70%)	0.99

* American College of Cardiology/American Heart Association lesion classification.

tion was diagnosed by an increase in creatine kinase-MB level to >3 times the upper limit of normal. Periprocedural increase in creatine kinase-MB (7.5% in patients who had DM vs 10.7% in those who did not, p = 0.19) was not included in the estimation of MACEs. Target lesion revascularization was defined as a repeat intervention or coronary artery bypass surgery in the same lesion that was treated in the index procedure. Stent thrombosis was diagnosed when thrombi were documented angiographically or sudden cardiac death occurred without definite cause.

Continuous variables are presented as means ± SD. Categorical variables are presented as frequencies. Comparisons were performed with Student's *t* test and chi-square or Fisher's exact test. Target lesion revascularization and MACEs during follow-up were analyzed by the Kaplan-Meier method. Log-rank test was used for survival comparison. All statistical tests were 2-tailed, and a p value <0.05 was considered statistically significant.

Overall baseline clinical and procedural characteristics are presented in Tables 1 and 2. Patients who had DM and those who did not had the same procedural success rate of 98.0%. Average hemoglobin A1c values were 8.4% and 7.7% in patients who had insulin-dependent DM and those who had non–insulin-dependent DM, respectively (p = 0.03). Six-month follow-up angiography was performed in 159 of 226 patients who had DM (70.4%) and in 428 of 560 patients who did not (76.4%, p = 0.09). Although patients who had DM had longer lesions (p <0.01) and smaller vessels (p <0.01), there were no significant differences in late loss (p = 0.31), late loss index (p = 0.11), and binary restenotic rate (p = 0.41) between patients who had DM and those who did not (Tables 3 and 4). Binary restenotic rates were also similar between patients who had DM and those who did not with respect to sirolimus-eluting stents (5.3% vs 4.1%, p = 0.64) and paclitaxel-eluting stents (24.1% vs 19.0%, p = 0.43). In multivariate analysis, no independent predictor of binary restenosis was identified. Nine-month clinical follow-up was available in 225 of 226 patients who had DM (99.6%) and in 557 of 560 patients who did not (99.5%, p = 1.00). Clinical outcomes at 9 months are listed in Table 5. Among patients who had DM, there was 1 sudden cardiac death (0.4%) that occurred 256 days after stent implantation. Similarly, 3 cardiac deaths (0.5%) were noted among patients who did not have DM. Event-free survival curves for MACEs and target lesion revascularization are shown in Figure 1. Angiographic and clinical data

Table 3
Quantitative coronary angiographic analysis

Variables	DM		p Value
	Yes (n = 299)	No (n = 705)	
Before procedure			
Lesion length (mm)	26.6 ± 15.6	23.4 ± 13.2	<0.01
Reference vessel diameter (mm)	2.86 ± 0.49	2.97 ± 0.49	<0.01
Minimal luminal diameter (mm)	0.93 ± 0.49	0.95 ± 0.54	0.65
Diameter stenosis (%)	67.5 ± 15.4	68.2 ± 17.2	0.59
After procedure			
Minimal luminal diameter (mm)	2.77 ± 0.49	2.88 ± 0.48	<0.01
Diameter stenosis (%)	2.2 ± 13.9	2.1 ± 13.5	0.89
Acute gain (mm)	1.85 ± 0.57	1.94 ± 0.60	0.03
Follow-up			
Minimal luminal diameter (mm)	2.40 ± 0.75	2.53 ± 0.74	0.04
Diameter stenosis (%)	9.9 ± 28.0	10.3 ± 23.7	0.87
Late loss (mm)	0.41 ± 0.63	0.36 ± 0.65	0.31
Late loss index	0.23 ± 0.38	0.18 ± 0.37	0.11

Table 4
Angiographic restenosis: frequency, location, and patterns

Variables	DM		p Value
	Yes (n = 208)	No (n = 536)	
In-segment restenosis	21 (10.1%)	44 (8.2%)	0.41
Proximal edge	8 (3.8%)	22 (4.1%)	0.87
In-stent	16 (7.7%)	28 (5.2%)	0.20
Distal edge	6 (2.9%)	9 (1.7%)	0.29
Restenotic pattern*	21	44	
Focal	13 (61.9%)	27 (61.4%)	0.97
Diffuse	6 (28.5%)	12 (27.3%)	0.91
Proliferative	1 (4.8%)	2 (4.5%)	1.00
Total occlusion	1 (4.8%)	3 (6.8%)	1.00

* Number of lesions.

according to treatment modalities in patients who had DM are listed in Table 6.

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In this study, patients who had DM compared with those who did not manifested similar 6-month angiographic and 9-month clinical results and preserved safety with DES implantation in patients who had DM, as reflected by zero in-hospital MACE and stent thrombosis. We also found that patients who had insulin-dependent DM had a higher angiographic restenotic rate and a greater late loss than did those who had non–insulin-dependent DM.

Smaller vessels and longer lesions in patients who had DM should have given these lesions some disadvantage in terms of restenosis compared with lesions in patients who did not have DM. However, the 2 groups had similar 6-month angiographic restenotic rates and late losses, and a similar incidence of target lesion revascularization might suggest a potent neutralization effect of DESs for the exaggerated in-stent neointimal proliferation that is commonly associated with DM. This potent antiproliferative effect has been well documented in several intravascular ultrasound studies.[1–3] The present results agree with those of the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions (SIRIUS) trial, the TAXUS IV trial, and the Randomized Study With the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (RAVEL) trial.[4–7] In our study, longer lesions (26.6 vs 14.4 mm in SIRIUS, 13.4 mm in TAXUS IV, and 9.6 mm in RAVEL) were included. In addition to a potent antiproliferative effect of DESs, there may have been a slightly greater acute gain (1.85 vs 1.69 mm in SIRIUS, 1.72 mm in TAXUS IV, and 1.49 mm in RAVEL) that contributed in part to the favorable outcomes in our patients who had DM. Although patients who had insulin-dependent DM had a higher restenotic rate and poorer clinical outcomes compared with patients who had non–insulin-dependent DM, insulin treatment itself might be a surrogate rather than a cause of such phenomena. That is, patients who received insulin might be in a more advanced state of coronary atherosclerosis and, hence, more prone to exaggerated in-stent neointimal proliferation be-

Table 5
Clinical outcomes at nine months

Variables	DM		p Value
	Yes (n = 225)	No (n = 557)	
Cardiac death	1 (0.4%)	3 (0.5%)	1.00
Nonfatal myocardial infarction	2 (0.9%)	6 (1.1%)	1.00
Stent thrombosis	2 (0.9%)	2 (0.4%)	0.33
In hospital	0 (0%)	2 (0.4%)	1.00
Up to 9 mo	2 (0.9%)	0 (0%)	0.08
Target lesion revascularization	10 (4.4%)	23 (4.1%)	0.84
Percutaneous coronary intervention	9 (4.0%)	20 (3.6%)	0.68
Coronary bypass surgery	1 (0.4%)	3 (0.5%)	0.95
MACEs	11 (4.9%)	27 (4.8%)	1.00
In hospital	0 (0.0%)	4 (0.7%)	0.58
Up to 9 mo	11 (4.9%)	23 (4.1%)	0.64

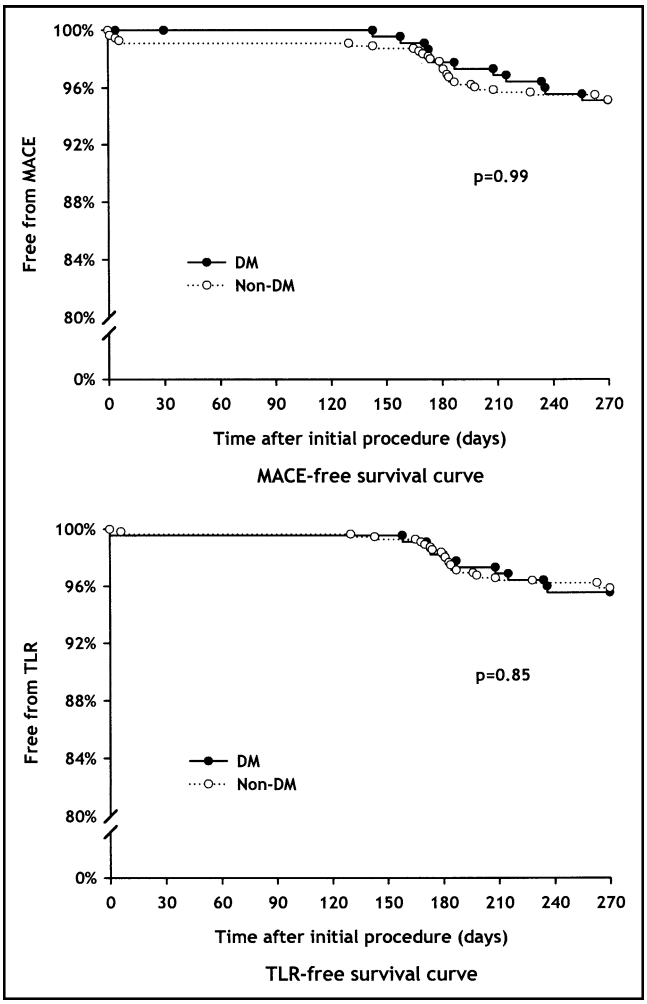

Figure 1. Event-free survival curves for patients who had DM and those who did not. TLR = target lesion revascularization.

Table 6
Insulin-dependent versus non–insulin-dependent diabete mellitus

Variables	Insulin-Dependent DM (n = 30)	Non–Insulin–dependent DM (n = 196)	p Value
Before procedure			
Reference vessel diameter (mm)	2.74 ± 0.42	2.87 ± 0.49	0.12
Lesion length (mm)	27.4 ± 15.2	26.5 ± 15.6	0.75
Minimal luminal diameter (mm)	0.99 ± 0.44	0.92 ± 0.49	0.43
Diameter stenosis (%)	64.2 ± 14.7	68.0 ± 15.5	0.16
After procedure			
Minimal luminal diameter (mm)	2.69 ± 0.43	2.77 ± 0.49	0.73
Diameter stenosis (%)	1.8 ± 12.5	2.7 ± 14.0	0.47
Acute gain (mm)	1.72 ± 0.63	1.85 ± 0.56	0.62
Angiographic follow-up*	20 (51.3%)	188 (72.3%)	
In-segment restenosis	5 (25.0%)	16 (8.5%)	0.04
In-stent restenosis	4 (20.0%)	12 (6.4%)	0.05
Late loss (mm)	0.83 ± 0.77	0.37 ± 0.60	0.02
Clinical follow-up	29 (96.7%)	196 (100%)	
MACEs	5 (17.2%)	6 (3.1%)	0.01
Target lesion revascularization	4 (13.8%)	6 (3.1%)	0.03

* Number of lesions.

yond the antiproliferative effect of DESs and subsequent adverse clinical events.

With respect to type of stent implanted, the restenotic rate was significantly higher in lesions that were implanted with paclitaxel-eluting stents than in those that were implanted with sirolimus-eluting stents in patients who had DM (23.1% vs 5.3%, $p < 0.01$) and those who did not (19.0% vs 4.1%, $p < 0.01$). There was no definitive cause that could explain this difference. Although consistent results concerning restenotic rate and clinical outcomes were not found in the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents in In-Stent Restenosis (ISAR-DESIRE),[8] Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents (ISAR-DIABETES), REALITY, and SIRTAX trials (these were presented at a meeting of the American College of Cardiology, Orlando, Florida, 2005), late loss was lower in patients who underwent sirolimus-eluting stent implantation than in those who underwent paclitaxel-eluting stent implantation. Other comparative trials are warranted to compare the efficacy of the 2 available DESs.

The limitations of this study should be addressed. First, the present study was a retrospective study that included a limited number of patients who had DM over a relatively short period. Second, angiographic follow-up was not performed completely. However, this study showed important information about real-world practice that DES implantation in patients who have DM may achieve similar angiographic and clinical outcomes as in patients who do not have DM.

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