

Comparison of Outcomes Using *Sirolimus*-Eluting Stenting in Diabetic Versus Nondiabetic Patients With Comparison of Insulin Versus Non-Insulin Therapy in the Diabetic Patients

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The effect of insulin therapy on adverse cardiovascular outcomes in diabetic patients has been debated and a reduced benefit in clinical restenosis outcomes after sirolimus stenting has been reported among diabetic patients requiring insulin therapy. We analyzed 297 diabetic patients receiving sirolimus-eluting stents, including 115 (39%) on insulin therapy, and compared outcomes with 541 nondiabetic patients treated consecutively during the same interval. The rates of target lesion revascularization (9.5% vs 3.5%, $p = 0.003$) and cardiac death or myocardial infarction (MI, 7.1% vs 3.1%, $p = 0.012$) were significantly higher for diabetic patients. Insulin treatment was independently associated with increased risk for target lesion revascularization (odds ratio [OR] 2.48, 95% confidence interval [CI] 1.22 to 5.00) and cardiac death or MI (hazard ratio [HR] 2.85, 95% CI 1.41 to 5.77), whereas the adjusted risk for diabetic patients not treated with insulin was not significantly different from patients without diabetes for target lesion revascularization (OR 1.32, 95% CI 0.66 to 2.62) or cardiac death or MI (HR 1.04, 95% CI 0.50 to 2.17). In conclusion, diabetes mellitus is associated with increased risk for target lesion revascularization and cardiac death or MI after receiving sirolimus-eluting stenting, and is significantly exaggerated by the requirement for insulin therapy. © 2007 Elsevier Inc. All rights reserved. (*Am J Cardiol* 2007;100:1187–1191)

Drug-eluting stenting has demonstrated a significant risk reduction in angiographic restenosis and target lesion revascularization (TLR) for diabetic patients, which is similar to the overall population,^{1,2} although the benefit was not evident for the small subgroup of diabetic patients requiring insulin therapy in the SIRoImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) trial.¹ A negative impact of insulin therapy on cardiovascular outcomes in diabetic patients has been debated, but most trials of coronary stenting have not had adequate numbers of these patients for comparison.

Methods

All consenting patients who underwent stent implantation with ≥ 1 sirolimus-eluting stents (Cypher, Cordis Corporation, Miami Lakes, Florida) at Beth Israel Deaconess Medical Center in the first 6 months after approval were prospectively enrolled in a follow-up registry to assess clinical outcomes at 9 to 12 months. All patients provided informed,

written consent to participate and the Institutional Review Board approved the study. Diabetes was defined based on a previous diagnosis requiring dietary or pharmacologic therapy at the time of the stent procedure. All patients were premedicated with 325 mg of aspirin to be continued indefinitely. Antithrombotic regimens, including intravenous heparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors were at the discretion of the treating physician. A loading dose of 300 mg clopidogrel was typically given in the cardiac catheterization laboratory, and 75 mg/day was recommended continuously for ≥ 3 months. Baseline clinical and procedural data were collected prospectively. Follow-up was obtained at a minimum of 9 months after the procedure using telephone contact with the patient and/or primary care physician and review of the electronic medical record.

A clinical events committee adjudicated all deaths, myocardial infarction (MI), and repeat revascularization procedures. All deaths were classified as cardiac unless a clear noncardiac cause was documented. All patients underwent assessment of cardiac enzymes at ~ 8 and ~ 16 hours after the procedure, and periprocedural MI was defined as creatine kinase-MB > 3 times the upper limit of normal; during follow-up, MI was defined as any elevation of creatine kinase-MB or troponin above normal with new onset of ischemic symptoms. TLR was defined as repeat percutaneous repeat revascularization or surgical bypass performed for restenosis of the stented segment, including the stent plus the 5-mm proximal and distal margins. The composite

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Table 1
Baseline patient characteristics

Clinical Characteristics	Diabetes Mellitus			Insulin Therapy		
	Yes (n = 297)	No (n = 541)	p Value	Yes (n = 115)	No (n = 182)	p Value
Age	65 ± 12	66 ± 12	0.22	62 ± 12	67 ± 11	0.001
Men	193 (65%)	395 (73%)	0.02	71 (62%)	122 (67%)	0.35
History of smoking	162 (55%)	248 (46%)	0.03	63 (55%)	99 (54%)	0.95
Current smoker	28 (9%)	79 (14%)	0.03	13 (11%)	15 (8%)	0.38
Body mass index (kg/m ²)	31.1 ± 7.1	27.8 ± 4.9	0.001	32.4 ± 7.9	30.2 ± 6.5	0.01
Hyperlipidemia	269 (91%)	434 (80%)	0.001	102 (89%)	167 (92%)	0.38
Hypertension	278 (94%)	414 (77%)	0.001	108 (94%)	170 (93%)	0.86
Renal insufficiency	60 (20%)	23 (4%)	0.001	30 (26%)	30 (16%)	0.04
Previous myocardial infarction	137 (46%)	159 (29%)	0.001	65 (57%)	72 (40%)	0.01
Left ventricular ejection fraction (%)	49.5 ± 11.9	53.4 ± 10.5	0.001	46.6 ± 13.5	50.1 ± 11.3	0.03
Acute coronary syndrome	128 (43%)	232 (42%)	0.95	49 (43%)	79 (43%)	0.95

Values are means ± SD or number of patients (percentages).

Table 2
Baseline procedure data

Variables	Diabetes Mellitus			Insulin Therapy		
	Yes (n = 362 lesions)	No (n = 660 lesions)	p Value	Yes (n = 134 lesions)	No (n = 227 lesions)	p Value
Multilesion treatment	65 (18%)	119 (18%)	0.98	20 (15%)	45 (20%)	0.44
Previous restenosis	36 (10%)	57 (9%)	0.48	9 (7%)	27 (12%)	0.11
Stent length (mm)	22.6 ± 14.3	23.0 ± 11.9	0.62	24.1 ± 18.1	21.8 ± 11.4	0.14
Final diameter stenosis <30%	361 (99%)	658 (99%)	0.17	133 (99%)	227 (100%)	0.99
Final TIMI 3 flow	361 (99%)	659 (99%)	0.33	133 (99%)	227 (100%)	0.99
Glycoprotein IIb/IIIa inhibitor	219 (74%)	416 (78%)	0.14	103 (76%)	165 (73%)	0.45

Values are means ± SD or number of patients (percentages).

TIMI = Thrombolysis In Myocardial Infarction.

end point of major adverse cardiac events (MACEs) was defined as the occurrence of cardiac death, MI, or TLR. Stent thrombosis was defined as acute ischemia with angiographic documentation of stent occlusion or thrombus or unexplained sudden death within 30 days.

Proportions were compared using chi-square or Fisher's exact tests. Continuous variables were compared using Student's *t* test. Event rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Multiple logistic regression was used to test the independent effects of insulin treatment and diabetes without insulin treatment on TLR, and Cox proportional hazards regression with censoring at the sooner of 9 months or at the time of the last follow-up was used to evaluate these effects on cardiac death or MI and MACEs. Other variables tested in the models were identified by baseline differences between diabetic and nondiabetic patients or diabetic patients requiring insulin treatment and other diabetic patients as well as previously identified and clinically logical predictors for each outcome. Variables that were significant at *p* < 0.10 in the univariate analyses were entered in the multiple variable model. For TLR, the tested variables included stent length, body mass index, stent diameter, chronic renal insufficiency, and current cigarette smoking. For cardiac death or MI, the other tested variables were age, gender, left ventricular ejection fraction, body mass index, previous MI,

Table 3
Secondary prevention medications at time of follow-up

Medications	Diabetes Mellitus		p Value
	Yes (n = 287)*	No (n = 487)*	
Aspirin	95%	95%	0.99
β blocker	86%	88%	0.27
ACE inhibitor or angiotensin receptor blocker	54%	58%	0.34
Statin	81%	87%	0.04
Clopidogrel ≥90 d	82%	87%	0.08
Clopidogrel ≥9 mo	70%	70%	0.98

* Patients with concomitant medication data at 9 to 12 months of follow-up.
ACE = angiotensin-converting enzyme.

hypercholesterolemia, hypertension, and chronic renal insufficiency. Missing data for left ventricular ejection fraction were imputed as the median value of nonmissing data by diabetes group. All statistical analyses were performed with SAS for Windows version 6.12 (SAS Institute, Cary, North Carolina).

Results

Baseline patient characteristics are shown in Table 1. Dia-

Table 4
Nine-month clinical events: diabetic versus nondiabetic patients

Events	Diabetes Mellitus		p Value
	Yes (n = 297)	No (n = 541)	
MACEs	33 (11.8%)	28 (5.6%)	0.002
Cardiac death	5 (1.8%)	6 (1.2%)	0.80
MI	17 (6.0%)	11 (2.2%)	<0.001
Cardiac death or MI	20 (7.1%)	16 (3.1%)	0.01
TLR	26 (9.5%)	17 (3.5%)	0.003
Stent thrombosis	6 (2.0%)	3 (0.6%)	0.049

All event rates determined by Kaplan-Meier method and compared using log-rank.

Values are number of patients (percentages).

Table 5
Nine-month clinical events: insulin-treated diabetic patients versus others

Events	Insulin Therapy		p Value
	Yes (n = 115)	No (n = 182)	
MACEs	19 (17.5%)	14 (8.2%)	0.001
Cardiac death	4 (3.7%)	1 (0.6%)	0.006
MI	9 (8.2%)	8 (4.6%)	0.06
Cardiac death or MI	11 (10.1%)	9 (5.2%)	0.01
TLR	14 (13.3%)	12 (7.1%)	0.04
Stent thrombosis	3 (2.6%)	3 (1.7%)	0.57

All event rates determined by Kaplan-Meier method and compared using log rank.

Values are number of patients (percentages).

betic patients were more often women and had higher prevalence of hypercholesterolemia, hypertension, chronic renal insufficiency, and previous MI. Body mass index was higher and left ventricular ejection fraction lower in diabetic patients. Diabetic patients requiring insulin treatment were younger, had higher body mass index, higher baseline percent hemoglobin A_{1C} (8.1 ± 1.4 vs 7.4 ± 71.4 , $p = 0.002$), and higher prevalence of chronic renal insufficiency and previous MI compared with diabetic patients not treated with insulin.

The number of narrowings treated and baseline procedural characteristics were similar between diabetic and nondiabetic patients (Table 2). These characteristics were not different between insulin-treated diabetic patients and those not treated with insulin.

During the follow-up period, compliance with secondary prevention pharmacologic treatments was high and similar for diabetic and nondiabetic patients (Table 3). The exceptions were use of statins, which was higher among nondiabetic patients, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which were used less frequently by both groups.

Median follow-up was 419 days with 92% of patients having ≥ 270 days of follow-up. Diabetic patients had significantly higher rates of cardiac death or MI and TLR, resulting in significantly higher overall MACEs (Table 4).

As shown in Table 5, overall MACEs and each component of MACEs were more frequent for insulin-treated diabetic patients. Results of multiple logistic and Cox propor-

Table 6
Results of logistic and proportional hazards multiple variable regression

Variables	Risk Ratio* (95% confidence interval)	p Value
TLR		
Diabetes requiring insulin	2.48 (1.22–5.00)	0.01
Diabetes not requiring insulin	1.32 (0.66–2.62)	0.42
Stent length (per 5 mm)	1.19 (1.09–1.30)	<0.001
Body mass index	1.04 (1.00–1.08)	0.06
Hypertension	3.29 (1.00–10.84)	0.06
Cardiac death or MI		
Diabetes requiring insulin	2.85 (1.41–5.77)	0.003
Diabetes not requiring insulin	1.04 (0.50–2.17)	0.96
Left ventricular ejection fraction (per 10%)	0.73 (0.57–0.94)	0.01
Age (per decade)	1.32 (1.03–1.70)	0.03
Chronic renal insufficiency	1.95 (1.01–3.80)	0.048
Hyperlipidemia	2.92 (0.90–9.41)	0.07
MACEs		
Diabetes requiring insulin	2.34 (1.33–4.10)	0.002
Diabetes not requiring insulin	0.99 (0.55–1.79)	0.96
Stent length (per 5 mm)	1.12 (1.03–1.21)	0.02
Left ventricular ejection fraction (per 10%)	0.82 (0.67–0.99)	0.048
Current smoking	0.42 (0.15–1.15)	0.09
Hyperlipidemia	2.18 (0.87–5.48)	0.10

* For target lesion revascularization = odds ratio; for cardiac death or myocardial infarction and major adverse cardiac events = hazard ratio.

tional hazard regression analyses are shown in Table 6. Insulin-treated diabetes mellitus was independently associated with TLR and cardiac death or MI as well as the combined end point of MACEs. Diabetes mellitus without insulin treatment did not have a significant association with any of the end points. Although there was a 30% higher adjusted risk for TLR among diabetic patients not treated with insulin relative to nondiabetic patients, this difference was not statistically significant and much less than the risk observed for insulin-treated patients. In an analysis restricted to diabetic patients, there remained an independent association of insulin treatment with TLR (odds ratio [OR] 2.24, 95% confidence interval [CI] 1.18 to 4.29, $p = 0.014$), cardiac death or MI (OR 2.68, 95% CI 1.20 to 5.99, $p = 0.017$), and MACEs (OR 2.72, 95% CI 1.45 to 5.49, $p = 0.002$). Baseline hemoglobin A_{1C} data were available for 155 patients (52%) and in separate models was not associated with any of the outcomes.

Discussion

In this study of unselected patients who underwent sirolimus-eluting stent implantation, diabetic patients had significantly higher rates of cardiac death or MI and TLR compared with nondiabetic subjects during the first 9 to 12 months. The higher risk for diabetic patients compared with nondiabetic patients is expected and similar to overall results of previous studies after balloon angioplasty and bare-metal stenting.^{3–9} These previous studies, however, did not evaluate differences in outcomes within the diabetic subgroup based on insulin treatment.

In our study, the adverse outcomes of TLR as well as cardiac death or MI were significantly associated with in-

sulin treatment, whereas diabetic patients not treated with insulin had TLR and cardiac death or MI outcomes that were not significantly different from nondiabetic patients. There are several potential explanations for observing a significant association between insulin therapy and adverse outcome. Because insulin is prescribed in type 2 diabetes mellitus when other measures of glycemic control have failed and usually late in the progression of disease due to an insulin secretory deficiency,^{10,11} such therapy may be a marker of more severe and longer term hyperglycemia. We did observe higher baseline hemoglobin A_{1C} among insulin-treated patients and the absence of an independent association of hemoglobin A_{1C} and adverse outcomes among patients for whom these data were available does not exclude this possibility as a major factor.

Nevertheless, there are several examples in animal and human studies where a direct effect of exogenous insulin on increased cardiovascular events has been postulated. Exogenous insulin administration results in increased neointimal proliferation after carotid artery balloon angioplasty in a rat model¹² and increased gene expression of interleukin-6 and tumor necrosis factor- α in adipose tissue of healthy volunteers.¹³ More recently, insulin treatment in type 2 diabetes mellitus has been associated with increased platelet aggregation,¹⁴ a finding of particular concern given current controversies about ongoing risk for stent thrombosis after drug-eluting stenting.

The relative merits of insulin therapy for improved glycemic control and theoretical harmful effects on vascular endothelium continue to be debated and available studies do not allow for firm conclusions.^{15,16} Regardless of these arguments, however, our study highlights the concern with analyses that include diabetes mellitus as a single variable. Despite numerous confounding variables, the requirement for insulin therapy clearly distinguishes patients who have significantly worse outcomes.

Outcomes stratified by insulin therapy have also been reported from several other studies. In the randomized SIRIUS trial, insulin-requiring patients had higher observed rates of TLR and MACEs than noninsulin requiring diabetic patients.¹ In the Taxus-IV trial of a paclitaxel-eluting stent, higher rates of overall MACEs, but not TLR, were observed for insulin-treated compared with non-insulin-treated diabetic patients.² Inference from the randomized trials is limited, however, by very small numbers of insulin-requiring patients and post-hoc analyses.

Several registry studies have reported conflicting results. Ong et al¹⁷ reported results in 293 diabetic patients from the nonconcurrent Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital [T-SEARCH] registries who received either sirolimus- or paclitaxel-eluting stents. Insulin-treated patients had a higher crude rate of major adverse cardiac events at 1 year compared with other diabetic patients (27.4% vs 14.6%, $p = 0.008$), but the difference was not significant after multivariable adjustment. More recently, Berenguer et al¹⁸ reported higher restenosis rates for insulin-treated diabetic patients after sirolimus-eluting stenting as well as a nonstatistically significant difference for the clinical outcome of target vessel failure (death, MI, or target vessel revascularization, 17.4%

vs 7.7%, $p = 0.07$). These investigators, however, also noted that insulin treatment was not a significant independent predictor of clinical outcome. Of note, these registry studies also had limited power to detect statistical significance with only 72 and 46 insulin-treated patients, respectively. In the largest reported study to date, the postmarketing voluntary e-Cypher Registry of >15,000 patients, both insulin-dependent (OR 2.25, 95% CI 1.60 to 3.13) and non-insulin-dependent diabetes (OR 1.43, 95% CI 1.06 to 1.90) were predictors of MACEs, whereas insulin-dependent diabetes was also a predictor of stent thrombosis (OR 2.76, 95% CI 1.71 to 4.29).¹⁹

The present study has several limitations. Angiographic follow-up was not obtained routinely and we cannot comment on an association between occlusive restenosis and increased risk for MI or cardiac death. We cannot exclude a type II error as the cause for failure to demonstrate a significant difference for diabetic patients not treated with insulin relative to nondiabetic patients. The definition for stent thrombosis required angiographic documentation and details of late deaths and MI were inadequate to exclude stent thrombosis as a contributor to these late outcomes. We also do not have baseline insulin levels, and, although almost all patients were diagnosed with type 2 diabetes mellitus, we cannot exclude an effect related to type 1 diabetes mellitus. Finally, these results are limited to the sirolimus-eluting stent, as we did not include paclitaxel-eluting stents in this cohort.

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