Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era

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Background Diabetes mellitus is associated with an increased risk of restenosis, stent thrombosis, and death after percutaneous coronary interventions. Little is known about the late outcome of patients with diabetes mellitus who receive drug-eluting stents (DES).

Methods This study includes a prospective database of 2557 consecutive patients with coronary artery disease who underwent DES implantation in native coronary arteries in 2 German hospitals. The primary end points of the study were mortality and clinical restenosis (target lesion revascularization). Secondary end points were binary angiographic restenosis, stent thrombosis, and the composite of death or myocardial infarction.

Results Within a median follow-up period of 2.3 years, stent thrombosis occurred in 14 patients with diabetes versus 17 patients without diabetes: 3-year Kaplan-Meier estimates of stent thrombosis were 2.2% versus 1.0%, with a relative risk of 2.17 (95% CI 1.09-4.33, $P = .027$). Binary angiographic restenosis was observed in 87 patients with diabetes and 208 patients without diabetes (15.2% vs 13.5%, $P = .32$). Target lesion revascularization was needed in 93 patients with diabetes and 219 patients without diabetes (12.8% vs 12.0%, $P = .56$). There were 93 deaths among diabetic patients versus 118 deaths among nondiabetic patients: 3-year Kaplan-Meier estimates of mortality were 17.3% versus 7.8%, with a relative risk of 2.10 (95% CI 1.61-2.74, $P < .001$). After adjustment in the multivariable analyses, diabetes remained an independent predictor of 3-year mortality with a hazard ratio of 1.63 (95% CI 1.23-2.17, $P < .001$), but not of angiographic ($P = .92$) or clinical restenosis ($P = .97$).

Conclusion Although DES attenuate diabetes-associated excess risk of restenosis, risk of death and thrombotic complications remains higher in patients with diabetes than in nondiabetic patients in the DES era. (Am Heart J 2007;154:688-93.)

Diabetes mellitus is a potent risk factor for the development and progression of coronary artery disease. Patients with diabetes represent roughly 25% of surgical revascularization and percutaneous coronary intervention (PCI) procedures.[1] Despite the advances in revascularization techniques and adjunct antithrombotic therapies, patients with diabetes show more unfavorable clinical outcomes compared with patients without diabetes.[2-7] In several randomized studies, drug-eluting stents (DES) were highly effective in reducing restenosis and the need of repeat revascularization in a broad range of subsets.[8-12] In patients with diabetes, DES have demonstrated a significant reduction in angiographic and clinical restenosis compared with bare-metal stents.[13] Previous studies comparing DES with bare-metal stents have demonstrated that the reduction in restenosis with DES was not associated with a similar reduction in mortality, myocardial infarction, or stent thrombosis.[10,14] However, the impact of diabetes on the angiographic and clinical outcome has not been assessed in a large number of patients with a long-term follow-up after treatment with DES. Therefore, we undertook this study to assess the impact of diabetes on long-term outcome in patients undergoing PCI with DES implantation.

Methods

Patients

Between August 2002 and June 2005, 2557 consecutive patients with stable or unstable coronary artery disease underwent a DES implantation (sirolimus-eluting or paclitaxel-eluting stent) in native coronary arteries at 2 centers, Deutsches Herzzentrum and 1.Medizinische Klinik rechts der Isar, Munich, Germany. Patients with an acute myocardial infarction (<72 hours) were not included in the study. All patients were asked to

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return for follow-up angiography at 6 months after the procedure. Diabetes was defined as active treatment with insulin or an oral antidiabetic agent or if the patient had an abnormal blood glucose level after an overnight fasting or abnormal glucose tolerance test results according to the World Health Organization criteria.[15] The population was divided into 2 groups according to the presence or absence of diabetes mellitus. Angina was graded according to Canadian Cardiovascular Society classification system.[16]

Intervention and adjunct drug therapy

All patients received a loading dose of 600 mg of clopidogrel at least 2 hours before undergoing coronary angiography.[17] One of two DES types—the paclitaxel-eluting stent (Taxus, Boston Scientific, Boston, MA) or the sirolimus-eluting stent (Cypher, Cordis, Johnson & Johnson, Miami Lakes, FL)—were used. The same type of DES was implanted if the patient needed >1 stent. Aspirin and unfractionated heparin were administered according to standard practice. After the intervention, the patients received aspirin 200 mg indefinitely and clopidogrel 150 mg for the first 3 days and 75 mg for ≥6 months. The use of additional antithrombotic drugs was at the discretion of the operators. β-Blockers, statins, nitrates, and angiotensin-converting enzyme inhibitors were given if clinically indicated.

Coronary angiographic evaluation

Baseline, postprocedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (Deutsches Herzzentrum) with an automated edge-detection system (CMS version 6.0, Medis Medical Imaging Systems, Nuenen, The Netherlands) by experienced operators unaware of the type of stent implanted.[17] The complexity of the lesions was classified according to the modified grading system of the American College of Cardiology–American Heart Association. Complex lesions were considered lesions of types B2 and C.[18] Measurements were performed on cineangiogram recorded after the intracoronary administration of nitroglycerin. The same single worst-view projection was used at all times. The contrast-filled nontapered catheter tip was used for calibration. The reference diameter was determined by interpolation. The variables that were measured included reference diameter of the vessel, minimal diameter of the lumen, diameter stenosis (difference between reference diameter and minimal luminal diameter, divided by reference diameter and multiplied by 100), and late lumen loss (difference between minimal luminal diameter at the end of the procedure and minimal luminal diameter at follow-up). Binary angiographic restenosis was defined as a diameter stenosis ≥50% at angiographic follow-up at 6 months measured at any point within the stented segment or in the 5-mm proximal or distal segments adjacent to the stent.

Study end points and follow-up criteria

Target lesion revascularization (clinical restenosis) and mortality at 3 years of follow-up were the primary end points of the study. Binary angiographic restenosis, stent thrombosis, and the composite of death or myocardial infarction were selected as the secondary end points. Adverse cardiac events were monitored throughout the follow-up period by a telephone interview at 30 days, a clinical visit at 6 to 8 months, and telephone interviews at 1-year intervals after procedure. If patients reported cardiac symptoms during the telephone interview, at least 1 clinical and electrocardiographic follow-up visit was performed at the outpatient clinic or by the referring physician. Relevant data were collected and entered into a computer database by specialized personnel at the clinical data management center. Information on mortality was obtained from hospital records, death certificates, or phone contact with relatives of the patient or attending physicians. The diagnosis of myocardial infarction during follow-up required the presence of new Q waves on the electrocardiogram or an elevation of creatine kinase level or its MB isoenzyme to ≥3 times the upper limit of the reference range in ≥2 blood samples. The criteria for target lesion revascularization included the presence of angiographic restenosis accompanied by symptoms and/or positive exercise test results. The diagnosis of stent thrombosis was always based on ischemia-driven coronary angiography showing intraluminal filling defect within the stent that resulted in TIMI grade 0 or 1 anterograde flow.

Table I. Baseline demographic, clinical, and angiographic characteristics

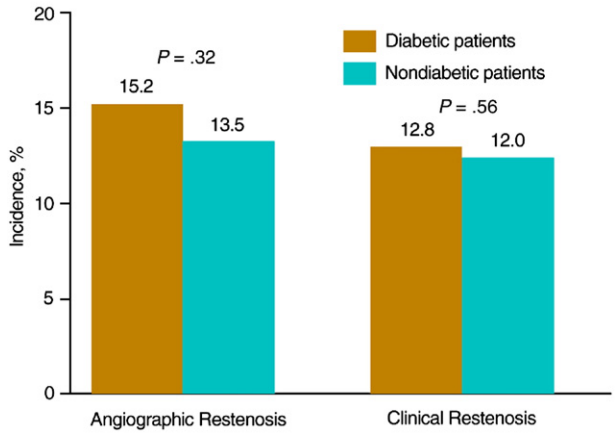
Variable	Diabetic patients (n = 727)	Nondiabetic patients (n = 1830)	P
Age (y)	68.2 ± 9.2	65.5 ± 10.8	<.001
Women (n [%])	199 (27.4)	362 (19.8)	<.001
Current smoker (n [%])	90 (12.4)	256 (14.0)	.28
Hypertension (n [%])	467 (64.2)	1031 (56.3)	<.001
Hyperlipidemia (n [%])	530 (72.9)	1326 (72.5)	.82
Angina class			.05
1	233 (32.1)	624 (34.1)	
2	219 (30.1)	566 (30.9)	
3	130 (17.9)	358 (19.6)	
4	145 (19.9)	282 (15.4)	
Prior myocardial infarction (n [%])	285 (39.2)	651 (35.6)	.09
Prior aortocoronary bypass surgery (n [%])	86 (11.8)	184 (10.1)	.19
Multivessel disease (n [%])	663 (91.2)	1489 (81.4)	<.001
Left ventricular ejection fraction (%)	52.6 ± 13.4	55.9 ± 12.4	<.001
Target vessel			.005
Left anterior descending (n [%])	304 (41.8)	814 (44.5)	.22
Right coronary artery, n (%)	152 (20.9)	462 (25.2)	.02
Left circumflex (n [%])	219 (30.1)	444 (24.3)	.002
Left main artery (n [%])	52 (7.2)	110 (6.0)	.29
Complex (type B2 or C) lesion (n [%])	563 (77.4)	1371 (74.9)	.18
Chronic total occlusion lesion (n [%])	50 (6.9)	144 (7.9)	.39
Vessel size (mm)	2.68 ± 0.56	2.75 ± 0.55	.002
Lesion length (mm)	13.6 ± 7.7	13.3 ± 7.6	.37
Minimum lumen diameter (mm)	1.06 ± 0.48	1.11 ± 0.50	.02
Diameter stenosis (%)	60.7 ± 15.1	60.1 ± 15.5	.49

Data are mean ± SD or counts (percentage).

Table II. Procedure-related characteristics

Variable	Diabetic patients (n = 727)	Nondiabetic patients (n = 1830)	P
Type of DES			.21
Sirolimus-eluting stent used (n [%])	392 (54.0)	1037 (57)	
Paclitaxel-eluting stent used (n [%])	335 (46.0)	793 (43)	
Abciximab therapy (n [%])	89 (12.2)	243 (13.3)	.48
Stent length (mm)	23.2 ± 9.5	22.7 ± 8.8	.21
Maximal balloon pressure (atm)	14.6 ± 3.0	14.6 ± 2.9	.86
Balloon-vessel ratio	1.15 ± 0.12	1.15 ± 0.12	.46
Mimimal lumen diameter (mm)	2.56 ± 0.49	2.65 ± 0.49	<.001
Diameter stenosis (%)	8.8 ± 7.3	8.1 ± 7.0	.03

Figure 1



Incidence of angiographic and clinical restenosis (target lesion revascularization).

Statistical analysis

Data are presented as mean ± SD or as counts or proportions (percentage). Continuous data are compared with the use of 2-tailed *t* test. Categorical data were compared with the use of χ^2 test or Fisher exact test when expected cell values were <5. Analysis of survival and survival free of myocardial infarction analysis were performed by applying the Kaplan-Meier method and log-rank test, which allowed the calculation of the relative risk (95% CIs) associated with diabetes. Multiple logistic regression analysis was used to identify independent correlates of the angiographic restenosis and target vessel revascularization (clinical restenosis). One lesion per patient chosen at random was entered into the patient-based analysis. The Cox proportional hazards model was used to assess the independent correlates of mortality. Variables entered into the multivariable models were age, sex, diabetes, arterial hypertension, smoking, hypercholesterolemia, angina class, multivessel disease, previous myocardial infarction, left ventricular ejection fraction, target vessel, complex lesions, chronic occlusion, restenotic lesion, vessel size, lesion length, diameter stenosis, total stented length, balloon-vessel ratio, balloon maximal pressure, and type of DES. All analyses were performed using S-Plus statistical package (Insightful Corp, Seattle, WA). A *P* value <.05 was considered to indicate statistical significance.

Results

Table I shows the baseline demographic, clinical, and angiographic characteristics of the patients. Of the 727 diabetic patients, 251 (34.5%) required insulin therapy. There were several differences between diabetic and nondiabetic patients, reflecting a higher risk profile of diabetic patients. Notably, diabetic patients presented a more advanced age, higher proportion of women, higher frequency of arterial hypertension and multivessel disease, lower ejection fraction, and smaller vessel size. Table II shows the procedural data and final angiographic results. With the exception of minimal lumen diameter (smaller in diabetic patients), the remaining procedure-related characteristics did not differ significantly among patients of both groups.

During the first 30 days after stenting procedure, there were 17 deaths (2.3%) among diabetic patients and 17 deaths (0.9%) among nondiabetic patients (*P* = .005). Myocardial infarction occurred in 28 patients (3.9%) with diabetes versus 50 patients (2.7%) without diabetes (*P* = .14). Thirty-day combined incidence of death or myocardial infarction was 5.1% (n = 37) among diabetic patients and 3.4% (n = 63) among nondiabetic patients (*P* = .05). Urgent reintervention due to ischemia was needed in 13 patients (1.8%) with diabetes and 9 patients (0.5%) without diabetes (*P* = .001).

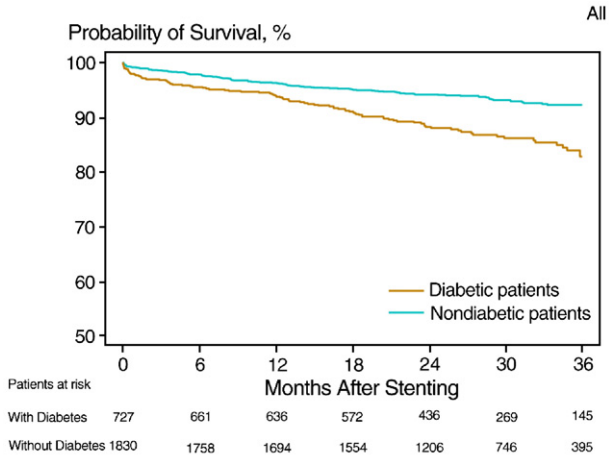
Angiographic outcome

Within the follow-up period, angiographic stent thrombosis occurred in 14 patients with diabetes versus 17 patients without diabetes: 3-year Kaplan-Meier estimates of stent thrombosis were 2.2% versus 1.0%, respectively, with a relative risk of 2.17 (95% CI 1.09-4.33, *P* = .027).

Follow-up angiography was performed in 574 diabetic patients (82.0% of eligible patients) and 1545 nondiabetic patients (86.0% of eligible patients, *P* = .03). Binary angiographic restenosis was observed in 87 patients with diabetes and 208 patients without diabetes (15.2% vs 13.5%, *P* = .32) (Figure 1). In-stent late lumen loss was 0.35 ± 0.54 mm among diabetic patients versus 0.34 ± 0.56 mm among nondiabetic patients (*P* = .76). Among diabetic patients requiring insulin therapy, in-stent lumen loss was 0.36 ± 0.54 mm.

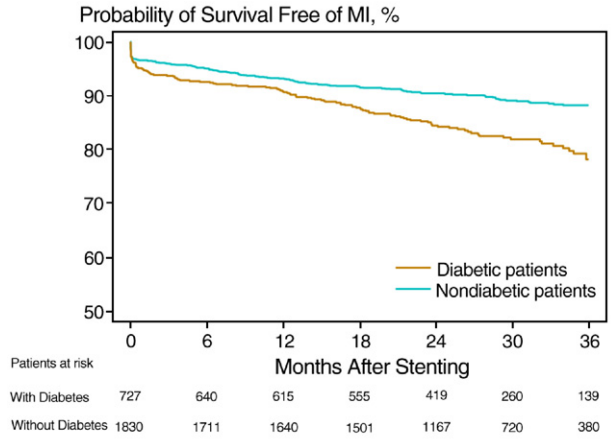
Multiple logistic regression analysis was used to identify independent correlates of binary angiographic restenosis. Independent correlates of angiographic restenosis were

Figure 2



Three-year probability of survival in patients with and without diabetes.

Figure 3



Three-year probability of survival free of myocardial infarction in patients with and without diabetes.

vessel size (χ^2 = 24.0, P < .001), balloon maximal pressure (χ^2 = 12.7, P < .001), type of DES (χ^2 = 5.8, P = .016), and chronic occlusion (χ^2 = 3.85, P = .049). Diabetes did not show an independent association with angiographic restenosis (χ^2 = 0.02, P = .92).

Long-term clinical outcome

The median (interquartile range) follow-up was 2.3 years (1.8-2.9 years) in diabetic patients versus 2.3 years (1.9-2.9 years) in patients without diabetes (Wilcoxon rank sum test P = .12). During the follow-up period, there were 93 deaths among diabetic patients versus 118 deaths among nondiabetic patients: 3-year Kaplan-Meier estimates of mortality were 17.3% versus 7.8%, respectively, with a relative risk of 2.10 (95% CI 1.61-2.74, P < .001) (Figure 2). The composite of death or myocardial infarction was 21.9% (n = 122) among diabetic patients versus 11.8% (n = 187) among nondiabetic patients (relative risk 1.73, 95% CI 1.38-2.16, P < .001) (Figure 3). Target lesion revascularization (clinical restenosis) was needed in 93 patients with diabetes and 219 patients without diabetes (12.8% vs 12.0%, P = .56) (Figure 1).

Multivariable analyses were used to identify independent correlates of 3-year target lesion revascularization (multiple logistic regression model) and 3-year mortality (Cox proportional hazards model). Independent correlates of target lesion revascularization were restenotic lesion (χ^2 = 16.0, P < .001), angina class (χ^2 = 9.6, P = .022), vessel size (χ^2 = 6.2, P = .013), and total stented length (χ^2 = 3.8, P = .05). Diabetes was not an independent correlate of target lesion revascularization (χ^2 = 0.01, P = .97). Cox proportional hazards model identified, diabetes, age, arterial hypertension, smoking, angina class, and left ventricular ejection fraction as independent predictors of 3-year mortality. Results of the Cox proportional hazards model for 3-year mortality are shown in Table III.

Table III. Independent predictors of 3-year mortality by Cox proportional hazards model

Variable	Hazard ratio (95% CI)	P
Diabetes	1.63 (1.23-2.17)	<.001
Age (for 10-y increase)	1.97 (1.68-2.31)	<.001
Smoking	2.15 (1.46-3.17)	<.001
Arterial hypertension	0.55 (0.41-0.73)	<.001
LV ejection fraction (for 10% decrease)	1.28 (1.16-1.41)	<.001
Angina class (class 4 vs class 1)	1.61 (1.07-2.43)	.014

LV, Left ventricular.

Discussion

The present study includes the largest series of patients to have received DES in "real-world" practice who have undergone routine follow-up angiography. With regard to in-stent restenosis, our data showed that DES implantation in patients with diabetes is associated with favorable results comparable to those achieved in patients without diabetes, clearly demonstrating the ability of DES to offset diabetes-associated increased risk of restenosis after PCI. This finding has been substantiated by both univariate and multivariable analyses, which did not identify diabetes as a predictor of increased risk of restenosis in this large consecutive series of patients treated with DES, although it is at odds with the results obtained in a recent, smaller cohort of 840 patients (211 diabetic patients)

treated with DES and followed up for 6 months by Hong et al.[19] Our study showed that patients with diabetes are at increased risk of death and thrombotic complications, and diabetes remained an independent predictor of mortality in the DES era. We were not able to make inferences about the relative efficacy of sirolimus-eluting or paclitaxel-eluting stents; stent selection was not made necessarily on the basis of a randomized study protocol.

The presence of diabetes mellitus is associated with an increased risk of restenosis, stent thrombosis, and death after PCI.[2,3,5,20] Several putative mechanisms, including increased intimal hyperplasia, higher coagulability, a higher inflammatory response, endothelial dysfunction, and comorbid conditions, have been postulated to account for poorer outcomes after PCI in diabetic patients.[1,4,21] Various studies have convincingly demonstrated that DES implantation results in a drastic reduction of coronary restenosis compared with bare-metal stents.[8-12] Although it has been demonstrated that DES implantation in patients with diabetes has the potential to markedly reduce in-stent restenosis,[13] the impact of DES on mortality, occurrence of myocardial infarction, or stent thrombosis in diabetic patients is unknown.

The incidence of early stent occlusion has been low (<1%) in patients treated with bare-metal stents and adequate antiplatelet therapy.[22] The presence of diabetes mellitus was recognized as a predictor of stent occlusion after bare-metal stent implantation.[2,5] Diabetes mellitus is strongly associated with loss of endothelial cells, increased platelet activation, hypercoagulability, and release of vasoconstrictive substances.[1,23] Randomized studies have shown that DES are superior to bare-metal stents regarding the risk of restenosis.[9-12] Iakovou et al[24] have demonstrated that the presence of diabetes is still an independent predictor of stent occlusion in the DES era. By reporting a greater incidence of stent thrombosis in patients with diabetes compared with nondiabetic patients, our study offers another evidence of diabetes-associated increased risk of stent thrombosis in patients treated by DES. This finding may have implications regarding antithrombotic therapy of patients with diabetes after DES implantation. Specifically, it may imply that diabetic patients who receive DES may be in need of a higher maintenance dose of clopidogrel[25] or alternative antiplatelet drug therapy. However, these implications need support by specifically designed studies.

Traditionally, an aggressive neointimal proliferation has been considered a major disadvantage of diabetic patients.[1,4] Previous studies have found diabetes mellitus to be a powerful independent predictor of restenosis after balloon angioplasty[26,27] or bare-metal stent implantation.[2,3] Diabetes has been the Achilles' heel of PCI in randomized studies directly comparing balloon angioplasty or bare-metal stenting and coronary artery bypass graft.[28,29] Recently, subset analyses from randomized trials[13,30] or specifically designed studies addressing the subset of diabetic patients[31] have clearly shown that DES markedly reduce the likelihood of restenosis in this high-risk group compared with bare-metal stents. The present study also shows that the negative impact of diabetes on restenosis is much weaker when current effective DES technology is used. These findings may indicate a change in the treatment of the challenging group of patients with diabetes and clinical coronary artery disease in whom DES along with glycemic control may become the therapy of choice. This therapeutic modality is being investigated against coronary artery bypass surgery in the ongoing FREEDOM randomized trial.[32]

The study does have some limitations. First, although by its design the study was a prospective registry of unselected patients, the study is not randomized and is only confined to DES. The study lacks a comparative arm of bare-metal stents, which would have allowed the assessment of potential differences in the long-term impact of diabetes between DES and bare-metal stents. Second, the nonrandomized design of the present study precludes any direct comparison between sirolimus-eluting and paclitaxel-eluting stents.

Conclusion

Our study shows that although DES abolish or attenuate diabetes-associated excess risk of restenosis in patients with coronary artery disease, the risk of death and thrombotic complications remains higher in diabetic patients compared with nondiabetic patients.

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