# Clinical Impact of Drug-eluting Stents in an Unselected Population of Diabetic Patients

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ABSTRACT

*Background:* Drug-eluting stents (DES) have been shown in randomized trials to reduce clinical events in diabetic patients. Our aim was to determine whether these clinical results are applicable in an unselected population of patients with non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM).

*Methods:* We studied 440 consecutive patients (271 NIDDM and 169 IDDM) who underwent percutaneous coronary intervention, divided into 2 cohorts: Group A (1998–2000): 220 patients with bare metal stents, and Group B (2002–2004): 220 patients with drug-eluting stents. We analyzed major coronary adverse events (death, nonfatal acute myocardial infarction, and target lesion revascularization) over a mean follow-up of $18 \pm 15$ months.

*Results:* Group B had more patients who were insulin-dependent (44.5 versus 32.3% $p<0.001$) or had hypertension (64.5 versus 54.1%; $p = 0.02$), a lower left ventricular ejection fraction (53.89 versus 56.8%; $p = 0.04$), more complex lesions (B2/C) (82.7 versus 62.3%; $p<0.001$), more treated lesions (1.40 versus 1.26; $p<0.001$), more stents implanted (1.69 versus 1.15; $p<0.0001$), and more patients treated with abciximab (76.8 versus 42.7%; $p<0.0001$). During the follow-up, Group B had fewer major adverse coronary events (11.7 versus 27.9%; $p<0.001$) and a reduction in target lesion revascularization (3.9 versus 17.2%; $p<0.001$), with no differences in death or myocardial infarction. Both groups experienced a significant reduction in events (NIDDM: 8.1 versus 26.7%; $p<0.001$ and IDDM: 16 versus 31.9%; $p = 0.016$). Multivariate regression analysis showed the use of drug-eluting stents to be in direct relation with event-free survival (odds ratio [OR]: 3.37; 95% confidence interval [CI], 1.44–7.90; $p = 0.005$).

*Conclusion:* Despite the worse angiographic characteristics, the use of DES reduced clinical events, particularly target lesion revascularization.

Key words: diabetes mellitus, revascularization, drug-eluting stents, prognosis

## Introduction

A high proportion of patients who undergo percutaneous coronary intervention (PCI) have diabetes mellitus. These patients have a worse prognosis after PCI, even in the era of stents,[1–5] due to the particular characteristics associated with coronary heart disease in diabetes.[6–8]

Although the introduction of new drug-eluting stents (DES) has revitalized the field of PCI due to the reduction in the rates of restenosis, certain high-risk populations, such as patients with diabetes, still have a high rate of complications following intervention.[9]

Information concerning the impact of DES in diabetic patients comes from subgroup analyses in large randomized clinical trials (Sirolimus-eluting stent in coronary lesions [SIRIUS][10] and TAXUS IV[11], a randomized study aimed at the diabetic population diabetes and sirolimus-eluting [DIABETES] trial)[12] and registries that suggest greater benefit associated with DES in complex lesions involving a greater risk of restenosis.[13] However, controversy exists concerning the benefit of DES in the subgroup of patients with insulin-dependent diabetes mellitus (IDDM), with a few studies suggesting a more modest benefit.[10,14]

Our aim was to assess the medium-term influence on the clinical outcome of the use of DES in comparison with standard bare metal stents (BMS) in an unselected population of diabetic patients undergoing PCI, and to evaluate whether the type of diabetes, IDDM or non-insulin-dependent diabetes mellitus (NIDDM) influences this outcome.

## Methods

We undertook an observational study of the effectiveness of DES in an unselected population of diabetic patients in comparison with historical controls. The study included 440 consecutive diabetic patients who underwent successful PCI, divided into two groups: Group A (1998–2000), 220 diabetic patients (149 NIDDM and 71 IDDM) treated with BMS, and Group B (2002–2004), 220 diabetic patients treated with DES (122 NIDDM and 98 IDDM), of whom

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109 received rapamycin-eluting stents and 111 paclitaxel-eluting stents. The study, design, and procedures complied with the Declaration of Helsinki. No exclusion criteria were applied, not even acute patients. Patients were considered to have diabetes if they had a previous diagnosis of diabetes, whether they were receiving oral antidiabetic agents or insulin. Data were recorded on the demographic, clinical, angiographic, and PCI characteristics. Multivessel disease was considered to be the involvement of 2 or 3 epicardial vessels >2 mm with stenosis >70%.

### Intervention Protocol

The PCI for stent implantation was performed by the usual method guided by visual analysis of the angiograms until an adequate angiographic result was obtained: residual lesion <30% with thrombolysis in myocardial infarction (TIMI) III flow. Intravenous heparin was administered at a dose of 100 U/kg, or 70 U/kg in the case of the concomitant use of abciximab, which was left to the criteria of the operator. All the patients received 100–300 mg of aspirin, as well as ticlopidine (250 mg twice daily) for 1 month in Group A, and clopidogrel (75 mg per day, with a loading dose of 300 mg for patients who had not taken it previously) in Group B for 3 months after implantation of a rapamycin-eluting stent, or 6 months after a paclitaxel-eluting stent.

### Adverse Events and Clinical Follow-up

Patients were followed-up in the cardiology office or by telephone. A coronary angiogram was ordered at the discretion of the physician in the case of symptoms or signs of myocardial ischemia. Major adverse events were considered to be cardiovascular death (sudden death, due to myocardial infarction, heart failure, or cerebrovascular accident), nonfatal myocardial infarction (precordial pain, with new Q-waves in at least 2 contiguous leads, and an increase in Cardiac creatine phosphokinase [CPK] of at least twice the normal laboratory range), and the need for revascularization of the treated vessel (considering both the treated segment as well as the 5 mm proximal and distal margins of the stent).

### Statistical Analysis

The qualitative variables are shown as the mean ± standard deviation. The quantitative variables are expressed as percentages. Qualitative variables were compared with the $\chi^2$ test (or Fisher's exact test if the expected frequencies were fewer than 5). The quantitative variables were compared using the Student's t-test. Cox multivariate regression analysis was used to evaluate those factors contributing to the final study outcome in both groups. The analysis included the following variables: age, sex, use of DES, insulin dependence, prior infarction, prior percutaneous revascularization, number of vessels, complete revascularization, length of the lesion, diameter of the vessel, ejection fraction <40%, and the use of abciximab. Event-free survival was analyzed by the Kaplan-Meier method. Statistical Package for Social Sciences (SPSS) version 12.0 for Windows was used (SPSS, Inc., Chicago, Ill., USA). Results were considered statistically significant if the $p<0.05$.

## Results

Table 1 shows the baseline characteristics. Group B contained more patients with IDDM, hypertension, and a prior PCI. Most of the revascularization procedures were undertaken during admission for acute coronary syndrome.

Regarding the angiographic characteristics (Table 2), multivessel coronary disease was common in both groups, with 28% of patients in each group having triple vessel disease. Group B had a worse left ventricular ejection fraction, a more unfavorable angiographic profile with lesions that were more complex (B2/C), longer, and more calcified, with more treated lesions and implanted stents per patient. Both groups had similar complete revascularization rates.

The clinical and angiographic features of the patients compared according to the type of diabetes (IDDM and NIDDM) are shown in Table 3. The IDDM group contained more women, and a greater number of patients with a previous infarction and more diffuse disease, with longer, more calcified, and more complex lesions.

The mean follow-up was 18 ± 15 months (median, 16 months), completed by 95.4% of the patients. We found a reduction in adverse events in Group B (11.7% versus 27.9%; $p<0.001$) (Table 4), with no differences in death or nonfatal myocardial infarction. No differences were detected in the rates of stent thrombosis (1.8% with BMS and 2.4% with DES). Group B experienced a significant reduction in revascularization of the treated lesion (3.9% versus 17.2%; $p<0.001$).

Analysis according to the type of diabetes showed that the NIDDM patients experienced an overall reduction in events from 26.7% to 11.7% ($p<0.001$) and the IDDM patients a reduction from 31.89% to 16% ($p<0.016$) (Table 5). The need for revascularization of the treated lesion was less in the NIDDM (17.8% versus 2.7%; $p<0.001$) than in the IDDM (15.9% versus 5.3%; $p = 0.024$).

The Cox multivariate regression analysis showed that the use of DES was directly related with event-free survival (odds ratio [OR], 3.37; 95% confidence interval [CI], 1.44–7.90; $p = 0.005$), as well as with the use of abciximab (OR, 2.59%–95% CI, 1.19–5.60; $p = 0.016$), whereas a previous myocardial infarction was inversely associated (OR, 0.44; 95% CI, 0.22–0.87; $p = 0.02$) (Table 6).


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TABLE 1: Baseline characteristics of the patients

| | Group A (BMS) n = 220 | Group B (DES) n = 220 | p |
|---|---|---|---|
| Age | 64.7 ± 8 | 65.1 ± 9 | NS |
| Female (%) | 39.5 | 36.8 | NS |
| Hypertension (%) | 54.1 | 64.5 | 0.026 |
| Smoking (%) | 43.6 | 41.8 | NS |
| Hyperlipidaemia (%) | 41.4 | 40.9 | NS |
| IDDM (%) | 32.3 | 44.5 | 0.001 |
| Previous PCI (%) | 3.6 | 13.6 | 0.001 |
| Previous CABG (%) | 4.5 | 3.2 | NS |
| Admission ACS (%) | 85 | 82 | NS |
| Previous myocardial infarction (%) | 59.1 | 51.4 | NS |
| PCI acute (%) | 2.7 | 3.2 | NS |
| Medical treatment | | | |
| Aspirin (%) | 95.4 | 93.2 | NS |
| Beta-blockers (%) | 62.7 | 67.2 | NS |
| RAA antagonist (%) | 75 | 78.4 | NS |
| Statins (%) | 62.2 | 68.3 | NS |
| Follow-up (months) | 19.3 ± 18 | 18.4 ± 9 | 0.1 |

Data are presented as mean ± SD or percentages. *Abbreviations:* ACS = acute coronary syndrome; BMS = bare metal stents; DES = drug-eluting stents; IDDM = insulin-dependent diabetes mellitus; RAA = renin-angiotensin-aldosterone; PCI = percutaneous coronary intervention.

## Discussion

Our study represents the largest series of "real-world" diabetic patients to date and shows that the use of DES was associated with a medium-term reduction in clinical events, as compared with a previous cohort treated with BMS. The main benefit was seen in the reduced need for revascularization of the treated lesion. The benefit was found in both subgroups (NIDDM and IDDM). The reduction was even possible despite the DES group having worse angiographic and clinical characteristics, demonstrating the neutralizing effect of these stents on the deleterious action of diabetes.[15]

### Drug-eluting Stents and Diabetes Mellitus: Clinical Trials

In the SIRIUS trial,[10] which included 279 diabetic patients (26% of the total), the angiographic characteristics of the general group were more favorable than those of our series: 19.7% with triple-vessel disease, vessel diameter of 2.75 mm, and length of the lesion 14.5 mm. The need for revascularization of the target vessel was lower in the diabetic patients (6.9% versus 22.3%; $p<0.001$), though this benefit was not seen in the subgroup of 82 patients with IDDM, who had a high rate of restenosis (35%).

The TAXUS IV trial,[11,16] with 318 diabetic patients (24.2% of total), had equivalent angiographic characteristics to the SIRIUS patients. At 1 year, the need for revascularization of the target vessel was 7.9% versus 21.6% in the NIDDM group ($p<0.005$) and, unexpectedly, lower, though not significantly so, in the IDDM patients (6.2% versus 19.4%; $p = 0.07$).

The DIABETES trial[12] included 160 diabetic patients and 221 lesions, 111 treated with DES and 110 with BMS. One third of the patients had IDDM. The vessel diameter was less than in previous studies (2.34 mm) and 80% of the


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TABLE 2: Angiographic characteristics of the patients

| | Group A (BMS) 1998–2000 (n = 220) | Group B (DES) 2002–2004 (n = 220) | p |
|---|---|---|---|
| Ejection fraction | 56.8 ± 15 | 53.9 ± 14 | 0.04 |
| Multivessel disease (%) | 56.4 | 65.5 | NS |
| Three-vessel disease (%) | 28.2 | 28.6 | NS |
| Left anterior descending (%) | 49.5 | 59.5 | NS |
| Right coronary artery (%) | 32.3 | 26.9 | NS |
| Left circumflex (%) | 18.2 | 13.6 | NS |
| Number lesions treated per patient | 1.26 ± 0.5 | 1.40 ± 0.59 | 0.001 |
| Complex lesions (B2/C) (%) | 62.3 | 82.7 | 0.001 |
| Lesion length (mm) | 14.02 ± 7.4 | 18.27 ± 12.2 | 0.001 |
| Calcified lesions (%) | 31.8 | 45 | 0.012 |
| Reference diameter (mm) | 2.92 ± 0.52 | 2.98 ± 0.30 | NS |
| Number of stents per patient | 1.15 ± 0.7 | 1.69 ± 0.9 | 0.001 |
| Complete revascularization (%) | 54.5 | 50.9 | NS |
| Abciximab (%) | 42.7 | 76.8 | 0.001 |
| Repeated angiography (%) | 21.9 | 17.6 | NS |

Data are presented as mean ± SD or percentages. *Abbreviations:* BMS = bare metal stents; DES = drug-eluting stents.

lesions were complex, 65% with multivessel disease, and 43% lesions >20 mm; these characteristics were closer to those of the patients in our series rather than in the large trials. A rapamycin-eluting stent was associated with a reduction in restenosis (7.3% versus 31.3%; $p<0.001$) and clinical events at 9 months (11.3% versus 36.3%; $p<0.001$), the benefit being reported in the IDDM patients as well. The reduction in clinical events in our series was slightly lower, although our follow-up was longer. The percentage of IDDM patients was greater, and more patients had a previous myocardial infarction.

### Drug-eluting Stents and Diabetes Mellitus: "Real-World" Registries

Data on the efficacy DES in the real world are derived from analysis of different registries. However, no registry has been designed to evaluate the impact of DES in the general population of persons with diabetes mellitus, while at the same time avoiding a selection bias. The largest registry is RESEARCH,[17] which included 508 consecutive patients (91 diabetic) treated with rapamycin-eluting stents who were compared with 450 patients (67 diabetic) treated with BMS during an earlier period. The results were favorable for the DES, despite a worse angiographic profile, with a reduction in revascularization of the target organ at 1 year (3.7% versus 10.9%; $p<0.001$). Nevertheless, in subgroup analysis, DES failed to reduce events in diabetic patients.

Others[14] have analyzed the usefulness of rapamycin-eluting stents in unselected patients with complex lesions: 133 nondiabetic patients, 52 NIDDM, and 46 IDDM. Although the rates of events and restenosis were greater in IDDM, the only predictor of an unfavorable course was female sex. The evolution of the nondiabetic patients was very similar to those with NIDDM. There was a trend toward a worse evolution, defined as failure of the treated target vessel at 1 year, in the IDDM group (17.4% versus 7.7%; $p = 0.07$).

These data gave rise to an interesting debate about whether insulin dependence is a marker of the efficacy of DES. In our study, the only predictors of clinical events were the use of DES, abciximab and a history of infarction, but not IDDM. The impact of DES was significant in both the NIDDM and the IDDM subgroups, although the reduction

TABLE 3: Baseline and angiographic characteristics of the NIDDM and IDDM patients

| | NIDDM (BMS) n = 149 | NIDDM (DES) n = 122 | p | IDDM (BMS) n = 71 | IDDM (DES) n = 98 | p |
|---|---|---|---|---|---|---|
| Age | 64.5 ± 8.5 | 65 ± 9.3 | NS | 65.1 ± 9.1 | 65.2 ± 9.4 | NS |
| Female (%) | 33.6 | 23.8 | 0.07 | 52.1 | 53.1 | NS |
| Smoking (%) | 48.3 | 50 | NS | 33.8 | 31.6 | NS |
| Hypertension (%) | 55 | 70.5 | 0.009 | 52.1 | 57.1 | NS |
| Hyperlipidaemia (%) | 45 | 42.6 | NS | 33.8 | 38.8 | NS |
| Previous myocardial infarction (%) | 57.7 | 55.7 | NS | 62 | 45.9 | 0.039 |
| Previous PCI (%) | 3.4 | 13.9 | 0.002 | 4.2 | 13.3 | 0.048 |
| Previous CABG (%) | 4 | 2.5 | NS | 5.6 | 4.1 | NS |
| Abciximab (%) | 34.9 | 71.3 | 0.001 | 59.2 | 83.7 | 0.001 |
| Ejection fraction | 58.2 ± 15.3 | 52.9 ± 14.7 | 0.06 | 54.1 ± 16.3 | 55.1 ± 13.1 | NS |
| Number vessels treated/patient | 1.17 ± 0.3 | 1.33 ± 0.5 | 0.06 | 1.25 ± 0.6 | 1.26 ± 0.6 | NS |
| Number stents/patient | 1.03 ± 0.6 | 1.6 ± 0.8 | 0.001 | 1.39 ± 0.8 | 1.81 ± 0.9 | 0.004 |
| Lesion length (mm) | 13.9 ± 7.2 | 16.18 ± 11.4 | 0.06 | 14.10 ± 7.9 | 20.88 ± 12.7 | 0.001 |
| Stent length (mm) | 18.8 ± 9.4 | 22.77 ± 12 | 0.02 | 19.5 ± 8.2 | 27.56 ± 14 | 0.003 |
| Reference diameter (mm) | 2.93 ± 0.5 | 3.01 ± 0.3 | 0.18 | 2.90 ± 0.4 | 2.95 ± 0.3 | NS |
| Complex lesions (B2/C) (%) | 60.4 | 77.9 | 0.002 | 66.2 | 88.8 | 0.001 |
| Calcified lesions (%) | 27.8 | 41.8 | 0.04 | 40 | 49 | 0.24 |

Data are presented as mean ± SD or percentages. *Appreviations:* BMS = bare metal stents; DES = drug-eluting stents; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus; PCI = percutaneous coronary intervention.

in revascularization in the treated vessel in the IDDM patients was slightly inferior.

An aspect that restricts the debate about the benefit or otherwise in patients with IDDM is the heterogeneity of the study populations and, probably, disparity in the indications for use of insulin in the diabetic patients. It may, therefore, be more appropriate to consider more objective parameters, such as metabolic control, duration of diabetes, or the presence of microangiopathic complications.

Another aspect to consider is the use of IIb/IIIa platelet inhibitors, which have a proven benefit in diabetic patients.[18,19] Although in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial,[19] the abciximab group showed a reduction in rates of death, myocardial infarction, and target lesion revascularization. A recent trial[20] using intracoronary ultrasound found no association between abciximab and a reduction in stent intimal hyperplasia in diabetic patients. In our study, the use of abciximab, higher in the DES group for historic reasons, and due to a greater complexity of the lesions treated, was protective of events in univariate and multivariate analysis.

## Limitations

This retrospective, observational cohort study is subject to the limitations inherent to the study design. Comparison with a historical control group can incorporate bias into the analysis. The effect of rapamycin and paclitaxel does not appear to be comparable in diabetic persons in relation to late luminal loss, although this has not been translated into clinical impact.[21] The antiplatelet regimen differed for historical reasons, as did the use of glycoprotein IIb/IIIa inhibitors. No systematic control angiography was performed, which may influence the rate of revascularization found. We were unaware of the data regarding glycemic


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TABLE 4: Adverse events during follow-up

| | Group A (BMS) 1998–2000 (n = 215) | Group B (DES) 2002–2004 (n = 205) | p |
|---|---|---|---|
| Major adverse coronary events | 60 (27.9) | 24 (11.7) | 0.001 |
| Death | 18 (8.4) | 13 (6.3) | NS |
| Nonfatal myocardial infarction | 9 (4.2) | 7 (3.4) | NS |
| Target lesion revascularization | 37 (17.2) | 8 (3.9) | 0.001 |

Data are expressed as the number of patients and the percentage of the total in brackets. *Abbreviations:* BMS = bare metal stents; DES = drug-eluting stents.

TABLE 5: Adverse events during follow-up in the NIDDM and IDDM groups

| | NIDDM (BMS) n = 146 | NIDDM (DES) n = 111 | p | IDDM (BMS) n = 69 | IDDM (DES) n = 94 | p |
|---|---|---|---|---|---|---|
| Major adverse coronary events | 38 (26.7) | 9 (8.1) | 0.001 | 22 (31.9) | 15 (16) | 0.016 |
| Death | 9 (6.2) | 6 (5.4) | NS | 9 (13) | 7 (7.4) | 0.23 |
| Nonfatal myocardial infarction | 5 (3.4) | 1 (0.9) | 0.18 | 4 (5.8) | 6 (6.4) | NS |
| Target lesion revascularization | 26 (17.8) | 3 (2.7) | 0.001 | 11 (15.9) | 5 (5.3) | 0.024 |

*Abbreviations:* BMS = bare metal stent; DES = drug-eluting stent; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus.

TABLE 6: Multivariate predictors of survival free of adverse events

| | OR | CI (95%) | p |
|---|---|---|---|
| Age | 1.05 | 0.54–2.06 | NS |
| Coated stent | 3.37 | 1.44–7.90 | 0.005 |
| Previous PCI | 0.97 | 0.21–4.30 | NS |
| Complete revascularization | 1.90 | 0.65–1.52 | 0.23 |
| Sex | 0.90 | 0.54–2.06 | NS |
| Number of vessels | 0.95 | 0.47–1.75 | NS |
| IDDM | 0.62 | 0.30–1.30 | 0.21 |
| LVEF <40% | 0.64 | 0.24–1.75 | NS |
| Lesion length | 0.97 | 0.93–1.01 | NS |
| Vessel diameter | 0.55 | 0.29–1.06 | NS |
| Previous infarction | 0.44 | 0.22–0.87 | 0.02 |
| Abciximab | 2.59 | 1.19–5.60 | 0.016 |

*Abbreviations:* CI = confidence interval; IDDM = insulin-dependent diabetes mellitus; LVEF = left ventricular ejection fraction; OR = odds ratio; PCI = percutaneous coronary intervention.

control in the patients and also the duration of their diabetes, which might also affect the results.

## Conclusions

The cohort of diabetic patients treated with DES experienced fewer clinical events during the medium-term follow-up, both those with NIDDM and those with IDDM, despite the presence of worse angiographic characteristics, as compared with the cohort treated with BMS during an earlier period.


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