Original Research

Long-Term Results After Drug-Eluting Stent Implantation in Diabetic Patients According to Diabetic Treatment

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Introduction: In this prospective, single-center study we assessed the long-term results after drug-eluting stent implantation in non insulin-dependent diabetic patients compared to insulin-dependent patients.

Methods: A total of 610 consecutive diabetic patients (mean age 65 ± 9 years) underwent percutaneous coronary intervention with drug-eluting stent implantation. They were classified into 2 groups according to their diabetic treatment: 1) non insulin-dependent patients (477); 2) insulin-dependent patients (133). The primary endpoint was the composite of death, non-fatal myocardial infarction, bypass surgery and target lesion revascularization.

Results: Clinical follow up for more than 12 months (median 29 months) was achieved in 597/610 patients (98%). The insulin-dependent group had more women (29% vs. 18%, p=0.003), as well as a higher incidence of multivessel disease (84% vs. 65%, p<0.0001) and ejection fraction <40% (16% vs. 9%, p=0.037) compared to the non insulin-dependent group. The in-hospital results were almost the same in both groups, except for the incidence of non-Q myocardial infarction and bleeding complications, which were more frequent in the insulin-dependent group (9.8% vs. 4.8%, p=0.03, and 1.5% vs. 0%, p=0.047, respectively). During clinical follow up, no significant differences in the incidence of death or non-fatal myocardial infarction were observed, but target lesion revascularization and bypass surgery were more frequent in the insulin-dependent group (8.5% vs. 3.4%, p=0.01, and 4.7% vs. 1.3%, p=0.01, respectively). The event-free survival was lower in the insulin-dependent group (hazard ratio: 0.52; 95% confidence interval, 0.31-0.85, p=0.01).

Conclusion: The implantation of drug-eluting stents in diabetics is associated with excellent in-hospital and long-term results. However, the long-term effectiveness in insulin-dependent patients is lower, because of the greater risk of new revascularization.

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Diabetes mellitus (DM) has become a major threat to human health. The number of people with diabetes has increased alarmingly in the past two decades and this figure is expected to rise to almost 350 million by 2025.[1] Diabetes mellitus, whether type 1 or type 2, is a very strong risk factor for the development of coronary artery disease (CAD).[2] Specifically, cardiovascular disease is responsible for 75% of all hospital admissions and 80% of deaths in diabetic patients.[3-5]

Coronary artery disease in diabetics exhibits distinctive characteristics that confer an increased risk, such as more diffuse and accelerated lesions, with longer lesion lengths, smaller vessel size and greater plaque burden.[6-8] Coronary artery revascularization in diabetics continues to be a challenge, as these patients represent almost 25% of surgical revascularization

and percutaneous coronary intervention (PCI) procedures[9] and have worse outcomes than patients without diabetes, irrespective of the invasive therapy they receive.[10-11] Unfortunately, PCI with bare metal stents (BMS) in these particular patients is associated with worse long-term outcomes and increased restenosis rates than in the non-diabetic population.[12-13] Despite resent therapeutic advances, such as new antiplatelet treatments and drug eluting stents (DES), outcomes for diabetics after PCI are still significantly worse than for non-diabetic patients, mainly because of higher restenosis rates.[14] Furthermore, patients requiring insulin for the treatment of diabetes are more susceptible to adverse cardiac events.[15] However, randomized trials that recruited broad samples of patients both with and without DM showed that the use of DES for treatment of *de novo* coronary lesions can provide improved clinical and angiographic outcomes relative to BMS.[16-17]

The purpose of this study was to assess the long-term results of DES implantation in non insulin-dependent compared to insulin-dependent diabetic patients.

Methods

Between June 20, 2002, and Dec 31, 2005, a total of 610 consecutive diabetic patients underwent PCI in our hospital, with implantation of at least 1 DES in their native coronary arteries or aortocoronary bypass grafts. The population was divided into 2 groups according to the diabetes treatment: 477 patients were treated with oral agents and were considered as non insulin-dependent (NID), whereas 133 were insulin-dependent (ID).

Eligible patients had a history of stable or unstable CAD, including acute myocardial infarction or silent ischemia proven by stress test, and manifest DM, proven by fasting glucose ≥126 mg/dl or oral glucose challenge ≥200 mg/dl after 2 hours, or DM treated with oral antidiabetic agent, insulin or both. PCI was the treatment of choice according to the attending cardiologists and *de novo* or restenotic lesions were targeted for treatment. Major exclusion criteria were hemorrhagic diathesis, contraindications to the use of aspirin and thienopyridines, coexisting conditions that limited life expectancy to less than 12 months, and lesions within an unprotected left main artery unless there was a need for emergency treatment.

Coronary stent procedure

Coronary intervention was performed according to standard techniques, including optional balloon dilation before placement of the stent, and one or more stents were used in order to cover the entire diseased segment. All patients were treated with oral aspirin (at least 100 mg daily) and clopidogrel (a loading dose of 600 mg was given as soon as possible during the procedure for those without pretreatment, followed by 75 mg daily) for at least 12 months; the use of dual antiplatelet medication for a longer period was encouraged but left to the physician's discretion. All patients were advised to maintain aspirin (≥100 mg/day) or alternately clopidogrel on a lifelong basis.

Angiographic success was defined as the achievement of residual in-segment stenosis of ≤20%, associated with TIMI 3 flow, in the absence of a dissection. Clinical success was defined as angiographic success without the occurrence of death, Q-wave myocardial infarction, or repeat target lesion revascularization (TLR) during hospitalization.

Follow up, endpoints and definitions

Clinical outcomes during follow up were obtained through serial telephone interviews by research fellows and entered into a dedicated database. The primary endpoint was the occurrence of major cardiac events, defined as the composite of all-cause death, non-fatal myocardial infarction (MI), bypass surgery (CABG) and TLR. Cerebrovascular accident, stent thrombosis (ST) and non-target lesion revascularization (NTLR) were considered as secondary endpoints.

TLR was defined as a repeat PCI to treat a luminal stenosis >50% within the stent or in the 5 mm proximal or distal segments adjacent to the stent; NTLR was defined as an intervention in another lesion due to disease progression. MI was defined as the development of new pathological Q waves in at least two contiguous leads, irrespective of the presence of typical symptoms, with an elevated creatine kinase MB fraction level or, in the absence of pathological Q waves, an elevation in creatine kinase MB fraction ≥3 times the upper limit of normal value. ST was defined as acute, early, late, and very late if the event occurred within the first 24 hours, 30 days, >1 month to 1 year, or >1 year, respectively. ST was considered as definite if there was angiographic confirmation plus any new ischemic symptoms or new ischemic ECG changes or positive cardiac biomarkers within 48 hours, or pathologic documentation at autopsy or in tissue from thrombectomy. ST was considered as probable in the case of any unexplained death within the first 30 days from stent implantation or any

MI related to the territory of the implanted stent, and as possible in any unexplained death after 30 days following intracoronary stenting. Bleeding complications included any major bleeding requiring transfusion, whereas pseudoaneurysm, arteriovenous fistula, dissection and thrombosis or emboli were considered as vascular complications.

Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables as counts and percentages. The differences between the groups were assessed with a two-sided chi-square test or Fisher's exact test for categorical data and Student's t-test for continuous data, after evaluation of normal distribution with the Shapiro-Wilk test. The Mann-Whitney test was used for continuous data that were not normally distributed. Time-to-event data are displayed according to the Kaplan-Meier method and the log-rank test was used to evaluate differences between groups. All statistical analyses were performed with the use of SPSS software (version 12.0, SPSS Inc., Chicago, IL, USA). Statistical significance was based on a value of $p<0.05$ (for two-tailed hypotheses).

Results

Baseline and procedural characteristics

Three types of DES were used in our population: sirolimus-eluting stents were implanted in 487 (80%), paclitaxel-eluting stents in 64 (10%), zotarolimus-eluting stents in 12 (2%), and a combination of DES in 47 (8%) patients**.** The baseline and procedural characteristics of our study patients are presented in Table 1. The ID group had more female patients ($p=0.003$), with a lower ejection fraction ($p=0.037$), and a significantly higher incidence of multivessel disease and incomplete revascularization ($p<0.0001$).

Table 1. Clinical and procedural characteristics. Data given as n (%) or mean ± SD.

Characteristic, n (%)	NID (n=477)	ID (n=133)	p
Age	64.8 ± 9.2	65 ± 9	0.6
Female gender	84 (17.6)	39 (29.3)	0.003
Risk factors:			
hypercholesterolemia (total cholesterol >200 mg/dl)	438 (92.0)	126 (94.7)	0.35
hypertension	375 (78.6)	106 (79.7)	0.9
smoking history	299 (62.7)	75 (56.4)	0.19
family history	180 (37.7)	48 (36.0)	0.76
Previous MI	202 (42.3)	56 (42.0)	1
Previous CABG	75 (15.7)	28 (21.0)	0.15
ACS at presentation	164 (34.4)	47 (35.3)	0.8
EF <40%	45 (9.4)	21 (15.8)	0.037
Multivessel disease	310 (65.0)	112 (84.2)	<0.0001
Total occlusion	54 (11.3)	15 (11.3)	1
Bifurcation treatment	37 (7.8)	8 (6.0)	0.57
Multivessel stenting	86 (18.0)	25 (18.8)	0.89
Complete revascularization	227 (47.6)	39 (29.3)	<0.0001
Stents / patient	1.52 ± 0.8	1.71 ± 0.9	0.2
Total stent length (mm)	27.1 ± 14.6	29.8 ± 17.6	0.3
Treated vessel:			0.6
LM	8 (1.4)	2 (1.2)	
LAD	234 (41.2)	68 (43.0)	
LCX	134 (23.6)	39 (24.7)	
RCA	160 (28.1)	38 (24.0)	
VG	25 (4.4)	6 (3.8)	
Arterial graft	0	1 (0.6)	
Ramus	7 (1.2)	4 (2.5)	

NID – non insulin-dependent diabetic patients; ID – insulin-dependent diabetic patients; CABG – coronary artery bypass grafting; PCI – percutaneous coronary intervention; MI – myocardial infarction; ACS – acute coronary syndrome; EF – ejection fraction; LM – left main coronary artery; LAD – left anterior descending artery; LCX – left circumflex artery; RCA – right coronary artery; VG – vein graft.

In-hospital results (Table 2)

Clinical success was similar in both groups and no significant differences in the incidence of in-hospital death, Q-wave MI or vascular complications were observed. There was no ST, CABG or repeat PCI before hospital discharge in either group. Non-Q MI and bleeding complications were observed more frequently in ID patients (p=0.032 and p=0.047, respectively).

Clinical follow up

Long-term follow up (≥12 months) was achieved in 597/610 patients (98%: 468/477 and 129/133 patients in the NID and ID groups, respectively). The median follow-up time was 29 months (interquartile range 20-40 months) for NID and 32 months (interquartile range 23-41 months) for ID (p=0.16). Approximately 93% of our population (552 patients) received combined antiplatelet treatment with aspirin and clopidogrel for at least 12 months, with no significant difference between the NID and ID groups (94% vs. 90.6%, respectively, p=0.18). Rates of all-cause death (Figure 1), non fatal MI, and secondary endpoints were similar among NID and ID patients (Table 3), whereas TLR (Figure 2) and CABG rates (Figure 3) were higher in the ID group. The composite of all-cause death, non-fatal MI, TLR or CABG, which was our primary endpoint, was 9.4% among NID vs. 17.8% among ID (Pearson χ^2=0.007), resulting in a better event-free survival curve in the NID group (hazard ratio, HR 0.52; 95% confidence interval, CI: 0.3-0.85, p=0.01, Figure 4).

ST occurred in 14 NID patients (3%) vs. 7 ID patients (5.4%), (p=0.18). With regard to the time of onset, there was no early ST in ID patients, whereas 2 patients from the NID group presented early ST (p=NS). Late ST was observed in 4 patients from each group

Table 2. In-hospital results. Data given as n (%).

In-hospital events	NID (n=477)	ID (n=133)	p
Clinical success	475 (99.6)	132 (99.2)	0.5
Death	0	1 (0.8)	0.2
Stent thrombosis	0	0	
Emergency CABG	0	0	
Repeated-PCI	0	0	
Q-wave MI	1 (0.2)	0	1.0
Non Q-wave MI	23 (4.8)	13 (9.8)	0.032
Vascular complications	5 (1.0)	0	0.59
Bleeding complications	0	2 (1.5)	0.047

Abbreviations as in Table 1.

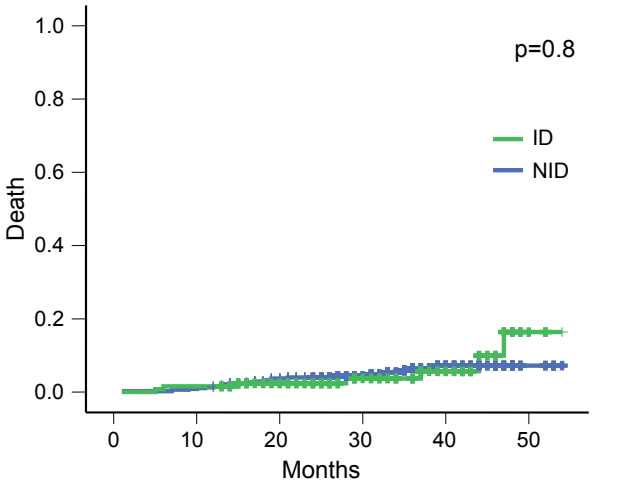

Figure 1. Cumulative rate of all-cause death.

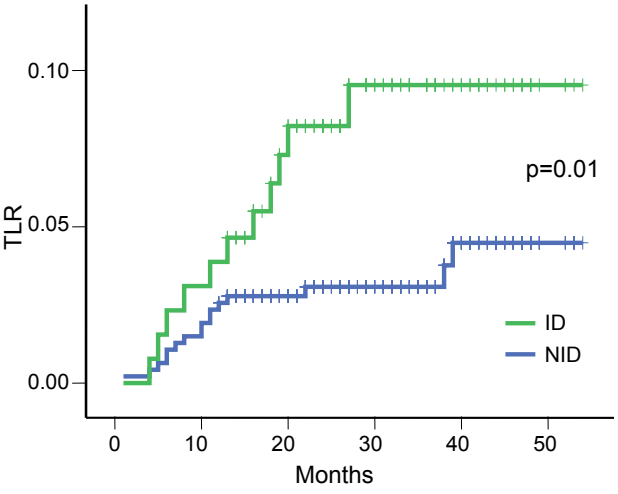

Figure 2. Kaplan-Meier estimates of target lesion revascularization.

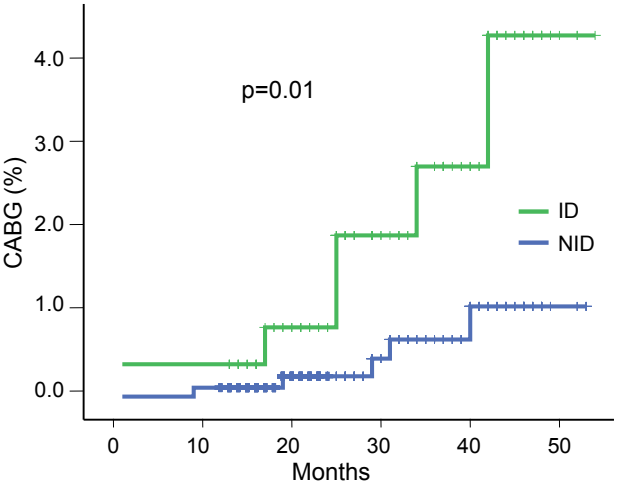

Figure 3. Cumulative rate of coronary artery bypass grafting.

Table 3. Long-term follow up results. Data given as n (%).

Clinical follow up	NID n=468 (98)	ID n=129 (97)	p
Primary endpoint:	44 (9.4)	23 (17.8)	0.007
Death	23 (4.9)	7 (5.4)	0.8
Non-fatal MI	6 (1.3)	4 (3.1)	0.2
CABG	6 (1.3)	6 (4.7)	0.016
TLR	16 (3.4)	11 (8.5)	0.013
Secondary endpoint:			
NTLR	76 (16.2)	23 (17.8)	0.66
CVA	10 (2.1)	1 (0.8)	0.47
Stent thrombosis:	14 (3.0)	7 (5.4)	0.18
definite	2 (0.4)	1 (0.8)	0.51
probable	1 (0.2)	1 (0.8)	0.38
possible	11 (2.4)	5 (3.9)	0.35
Any revascularization	86 (18.4)	35 (27.1)	0.029

TLR – target-lesion revascularization; NTLR – non target-lesion revascularization; CVA – cerebrovascular accident. Other abbreviations as in Table 1.

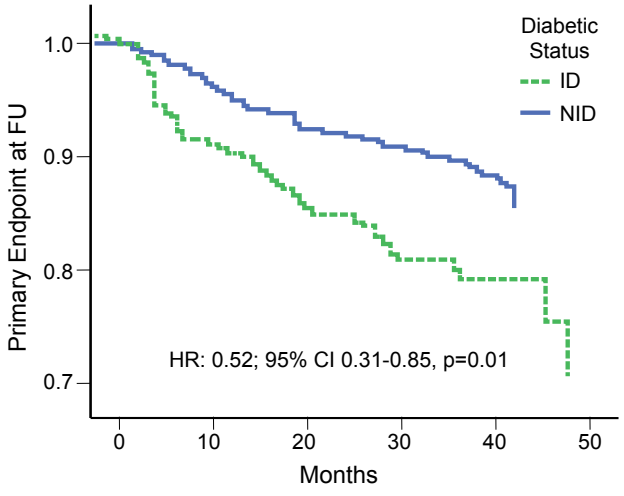

Figure 4. Event-free survival. FU – follow up; HR – hazard ratio; CI – confidence interval.

(p=0.05), but there were no significant differences in the incidence of very late ST between NID and ID patients (8/14 vs. 3/7, p=0.5). Similarly, no significant differences were observed in the incidence of definite, probable or possible ST between the NID and ID groups (0.4% vs. 0.8% p=0.5, 0.2% vs. 0.8% p=0.3, and 2.4% vs. 3.9% p=0.3, respectively).

Discussion

The principal findings of the present study indicate that ID patients have a less favorable clinical outcome compared to NID, mainly because of a greater risk of repeat revascularization. Adverse events such as death and MI were almost the same and were comparable in both groups, but event-free survival was worse in ID patients as a result of the need for repeat revascularization with either PCI or CABG. No differences in the incidence of NTLR, cerebrovascular accident and ST were observed between the two groups.

Diabetes mellitus is associated with an increased atherothrombotic risk.[18] Atherothrombotic disease is accelerated in subjects with type 1 and 2 DM, accompanied by diverse underlying mechanisms, despite the common trace of hyperglycemia. The main feature of type 2 DM is insulin resistance, which precedes the development of hyperglycemia.[19] In contrast, in type 1 DM, hyperglycemia is the dominant abnormality, with insulin resistance appearing in longer-standing patients who develop renal disease.[20] Insulin resistance and hyperglycemia have several important effects, altering coagulation and platelet function and contributing to a prothrombotic status.

Even though the implantation of DES in diabetic patients may provide a reduced risk of restenosis and TLR,[21,22] DM remains a significant risk factor for restenosis after both BMS and DES implantation.[14] The higher rates of repeat revascularization and mortality after PCI in diabetic patients are mediated by two processes: restenosis and disease progression. These processes are affected in part by the metabolic dysregulation resulting from chronic hyperglycemia and insulin resistance.[23] There are a number of mechanisms that can explain the higher restenosis rate in diabetic patients. Hyperglycemia, which is the dominant abnormality in ID patients as mentioned above, directly causes endothelial dysfunction by decreasing the production of endothelium-derived relaxing

factor,[24] increasing oxidative stress by vascular protein glycation[25] and free radical formation,[26] and decreasing prostacyclin production.[27] Also, lipoprotein abnormalities[28] may impair endothelium-dependent relaxation;[29] moreover, a greater growth factor stimulation occurs in diabetics.[25,30] All these mechanisms may also lead to pronounced intimal hyperplasia, the main mechanism of restenosis in diabetic patients.[31]

The effectiveness of DES, especially in ID patients, has been a matter of debate. In the RESEARCH registry,[32] diabetic patients constituted one of the few subgroups in which evidence of benefit did not reach statistical significance and diabetes mellitus remained an independent predictor of adverse events and clinically driven target vessel revascularization (TVR). Similarly, in a Greek study, only DM was an independent predictor for angiographic restenosis after sirolimus-eluting stent implantation.[33] Furthermore, in a meta-analysis of 4 trials specifically addressing the effects on restenosis of implanting BMS or DES in diabetic and non-diabetic patients, DM remained an independent risk factor for restenosis,[14] suggesting that the use of DES does not completely bridge the gap between diabetics and non-diabetics.

In a recent real-world multicenter registry, no benefit was demonstrated among ID patients after DES implantation, whereas NID showed substantial improvements in the 2-year relative risk of major adverse cardiac events and TVR.[34] Similarly, the SIRIUS trial failed to demonstrate a benefit from sirolimus-eluting stent use in the subgroup of ID patients, owing to the high incidence of edge effect.[35] In accordance with our findings are the results from another single-center study, where patients who had insulin-dependent DM manifested a higher prevalence of restenosis compared with patients who did not require insulin for their diabetes treatment.[15] Likewise, in the EVASTENT matched-cohort registry, insulin therapy was an independent predictor of TLR.[36] In contrast, the DIABETES trial has demonstrated similar repeat revascularization rates among both NID and ID patients.[21]

An increasing severity of CAD in diabetic patients is associated with higher mortality.[37,38] In the present study there was no significant difference in the incidence of death between the two groups. Our results are similar to those from a pooled analysis of 5 randomized trials, where rates of all-cause mortality, cardiac and non-cardiac death were similar for DES and BMS in ID and NI patients.[39] In contrast, Ortolani et al[34] reported insulin-dependent DM as an independent predictor of all-cause death/acute MI at 2-year follow up. Moreover, in a very recent study, insulin use was an independent predictor for death, TVR and composite outcome (death, nonfatal MI, or TVR).[40]

ST remains a major concern after DES implantation, especially in diabetic patients.[38,41] The increased risk in diabetic patients might be related to the prothrombotic status typical of this population, but the non-responsiveness to antiplatelet therapy also has a role: diabetics have been considered clinically unresponsive to the cardioprotective effects of aspirin and clopidogrel.[42] In the present study there were no significant differences in the incidence of ST among patients treated with insulin or oral agents. Generally, ST is a rare complication and our study may be underpowered to demonstrate such differences. Although the overall ST rate was similar in both groups in our study, more ID patients than NID presented late ST. In the e-Cypher registry, insulin-treated DM, among other factors, was recognized as a clinical predictor of ST at 12 months.[43] Similarly, in the EVASTENT Matched-Cohort Registry, in addition to the interruption of antithrombotic treatment, insulin-requiring diabetes was among the independent ST predictors.[36]

Although the death and non-fatal MI rates were similar in both groups in the present study, the event-free survival was lower in ID patients, mainly as a result of the greater risk of new revascularization. The ID group had more female patients, with a higher prevalence of multivessel disease and incomplete revascularization, and all these factors may in part explain the worse outcome of this group, as several studies have reported an increased severity of CAD in female diabetic patients.[44] More female patients were included in the insulin requiring group in the EVASTENT Matched-Cohort Registry, where higher event rates for both safety and efficacy parameters were observed.[36] In another clinical study, Elezi et al[12] reported that diabetic patients receiving insulin had a trend for a lower event-free survival as compared to diabetic patients receiving hypoglycemic therapy or diet alone; however, this subgroup analysis could be underpowered to detect significant differences.

Study limitations

This is a single-center, nonrandomized study in which the decision about stent type was determined by the availability of the particular type of stent and the physician's discretion. Paclitaxel- and zotarolimus-elut-

ing stents were used 1 and 2 years later, respectively, than were sirolimus-eluting stents. The comparison of outcomes based on the type of the implanted stent was beyond the scope of our study. Furthermore, the study lacks a comparative arm of BMS, which would have allowed the assessment of potential differences between DES and BMS.

The creation of the two groups was based on the mode of treatment of the patients at admission and not on a careful study of whether they had type 1 or type 2 DM.

Conclusions

In this real-world diabetic population, the implantation of DES was associated with excellent in-hospital and long-term results. However, the long-term effectiveness in ID patients was lower because of an increased risk for new revascularization.

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