Original Studies

One-Year Clinical Outcomes After Sirolimus-Eluting Coronary Stent Implantation in Diabetics Enrolled in the Worldwide e-SELECT Registry

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Background: Diabetes mellitus has worse outcome after percutaneous coronary intervention. Aim: We assessed stent thrombosis (ST), major adverse cardiac events (MACE), and major bleeding rates at 1 year after implantation of sirolimus-eluting stents (SES) in patients with diabetes mellitus in a large multicenter registry. Methods: From May 2006 to April 2008, 15,147 unselected consecutive patients were enrolled at 320 centers in 56 countries in a prospective, observational registry after implantation of ≥1 SES. Source data were verified in 20% randomly chosen patients at >100 sites. Adverse events were adjudicated by an independent Clinical Event Committee. Results: Complete follow-up at 1 year was obtained in 13,693 (92%) patients, 4,577

Additional Supporting Information may be found in the online version of this article.

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(30%) of whom were diabetics. Within diabetics, 1,238 (9%) were insulin-treated diabetics (ITD). Diabetics were older (64 vs. 62 years, $P < 0.001$), with higher incidence of major coronary risk factors, co-morbidities, and triple-vessel coronary artery disease. Coronary lesions had smaller reference vessel diameter (2.88 ± 0.46 vs. 2.93 ± 0.45 mm, $P < 0.001$) and were more often heavily calcified (26.1% vs. 22.6%, $P < 0.001$). At 1 year, diabetics had higher MACE rate (6.8% vs. 3.9%, $P < 0.001$) driven by ITD (10.6% vs. 5.5%, $P < 0.001$). Finally, diabetics had significant increase in ST (1.7% vs. 0.7%, $P < 0.001$), principally owing to ITD (3.4% vs. 1.1%, $P < 0.001$). There was an overall low risk of major bleeding during follow-up, without significant difference among subgroups. Conclusions: In the e-SELECT registry, diabetics represented 30% of patients undergoing SES implantation and had significantly more co-morbidities and complex coronary lesions. Although 1-year follow-up documented good overall outcome in diabetics, higher ST and MACE rates were observed, mainly driven by ITD.

Key words: percutaneous coronary intervention; sirolimus-eluting stent; diabetes mellitus; stent thrombosis; antithrombotic therapy; bleeding complications

INTRODUCTION

Despite the markedly lower incidence of restenosis associated with drug-eluting stents (DES) as compared with bare-metal stents in patients with diabetes mellitus (DM) after percutaneous coronary intervention (PCI), the more complex coronary anatomy, prothrombotic and inflammatory state, and associated cardiovascular risk factors of diabetics remain independent predictors of unfavorable clinical outcomes [1]. Although insulin-treated DM is associated with high target lesion revascularization (TLR) rates after bare-metal stent implantation [2] and is an independent predictor of stent thrombosis (ST) [3], the impact of non–insulin-treated vs. insulin-treated DM on DES restenosis is less clear. Moreover, the analysis of interaction between different baseline cardiovascular risk profiles and prolonged dual antiplatelet therapy (DAPT) with the ongoing risk of ST, recurrent ischemia, and bleeding after DES use in routine interventional practice is still a debated problem and a challenging task, requiring large, unselected populations of diabetic patients with sufficient follow-up.

The e-SELECT registry is a large, multicenter, international clinical registry of "all-comer" patients with coronary artery disease undergoing PCI with the Cypher sirolimus-eluting stent (SES) [3]. This report presents the findings in the diabetic patient group enrolled in the e-SELECT registry, evaluating the interaction between baseline DM treatment (insulin use vs. no insulin) and outcome. Although first-generation SES have been replaced by newer stent designs eluting different antiproliferative drugs, a relatively large number of second-generation DES are still coated with sirolimus and are currently used in patients with DM [4]. Accordingly, the e-SELECT registry data may serve as a clinical benchmark for future comparative effectiveness analyses and may improve our clinical understanding of PCI long-term results in the DM population.

METHODS

The details of the e-SELECT registry, which enrolled 15,147 patients at 320 medical centers in 56 countries, have been published elsewhere [3]. In brief, baseline data were collected electronically at each participating center between May 2006 and April 2008 in consecutive, eligible patients who underwent implantation of ≥ 1 Cypher Select® or Cypher Select Plus® SES (Cordis Corp., Bridgewater, NJ) according to standard clinical practices and procedural techniques. The data included demographic information, cardiovascular history, co-morbidities, operator-defined lesion characteristics, procedural details, and antithrombotic regimen [5]. Patients were followed-up at 30, 180, and 360 days by telephone, office visit, or by contact with primary physicians or referring cardiologists. Data were transferred to an independent data management organization, analyzed by an independent Clinical Event Committee, and monitored for accuracy by an independent organization in 20% of the overall sample.

End Points and Supervision of the e-SELECT Registry

The primary end point of the registry was a composite of definite and probable ST at 1 year of follow-up, as defined by the Academic Research Consortium [6]. The secondary end points at 1 year included major bleeding according to the *Safety and Efficacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention: An International Randomized Evaluation* definition [7], cardiac and noncardiac death, myocardial infarction (MI), and major adverse cardiac events (MACE) defined as death from any cause, MI, and TLR.

TABLE I. Baseline Characteristics of Insulin-Treated and Non–Insulin-Treated Diabetics Vs. Nondiabetics

	Diabetics			
	Insulin-treated ($n = 1,238$ patients)	Non–insulin-treated ($n = 3,339$ patients)	Nondiabetics ($n = 10,506$ patients)	P*
Age, years	63.4 ± 9.9	63.7 ± 10.1	61.5 ± 11.1	<0.001
Men	768 (62.0)	2,475 (74.1)	8,130 (77.4)	<0.001
Body mass index ≥ 30	471 (38.0)	1,062 (31.9)	2,140 (20.4)	<0.001
History of:				
Myocardial infarction	487 (39.3)	1,074 (32.2)	3,293 (31.3)	<0.001
Percutaneous coronary intervention	449 (36.3)	1,055 (31.6)	3,346 (31.8)	ns
Coronary artery bypass grafting surgery	164 (13.2)	351 (10.5)	855 (8.1)	<0.001
Hypertension	981 (79.2)	2,589 (77.5)	6,601 (62.8)	<0.001
Hyperlipidemia	921 (74.4)	2,461 (73.7)	6,907 (65.7)	<0.001
Current smoking	170 (13.7)	529 (15.8)	2,331 (22.2)	<0.001
Peripheral vascular disease	171 (13.8)	255 (7.6)	515 (4.9)	<0.001
Cerebral vascular accident	99 (8.0)	190 (5.7)	354 (3.4)	<0.001
Serum creatinine > 177 μmol/L	99 (9.0)	69 (2.3)	172 (1.9)	<0.001
Chronic obstructive lung disease	76 (6.1)	147 (4.4)	374 (3.6)	<0.001
Mean Charlson index score	2.7 ± 1.8	1.9 ± 1.2	0.6 ± 0.9	<0.001
Charlson index score ≥ 3	532 (43.0)	640 (19.2)	374 (3.6)	<0.001
Preprocedural AVK therapy	33 (2.7)	64 (1.9)	199 (1.9)	ns
Indications for index procedure				
Stable angina	491 (39.7)	1,328 (39.8)	4,487 (42.7)	<0.001
Unstable angina	332 (26.8)	889 (26.6)	2,699 (25.7)	ns
Myocardial infarction	219 (17.7)	598 (17.9)	1,926 (18.3)	ns
Silent ischemia/others	196 (15.8)	524 (15.7)	1,394 (13.3)	<0.001
Triple vessel coronary artery disease	309 (25.0)	668 (20.0)	1,640 (15.6)	<0.001
Target vessel				
Left anterior descending artery	746 (47.1)	2,127 (49.1)	7,074 (52.1)	<0.001
Circumflex artery	373 (23.5)	1,056 (24.4)	2,853 (21.0)	<0.001
Right coronary artery	437 (27.6)	1,113 (25.7)	3,509 (25.8)	ns
Saphenous vein graft	33 (2.0)	103 (2.3)	178 (1.3)	<0.001

Values are mean ± SD or number (%) of observations.
*All diabetics vs. nondiabetics.
AVK, antivitamin K.

A Steering Committee planned the analysis, presentations, and publications of the e-SELECT results. The algorithms used to classify clinical events and the criteria used for MACE adjudication were developed by a Clinical Event Committee composed of interventional cardiologists who were not associated with the sponsor and were not participants in the registry [3]. The Committee also adjudicated all MACE, deaths, ST, and major bleeding.

Statistical Analysis

For all patients, standard descriptive statistics were used for baseline lesion and procedural characteristics and for clinical results. Continuous variables are presented as means ± standard deviations, medians, and ranges and were compared among groups using t-test or Wilcoxon rank–sum test as appropriate. Categorical variables are presented as numbers and percentages and were compared using χ^2 test or Fisher's exact test as appropriate. Cumulative rates of adverse clinical events were calculated using event-specific adjusted denominators. Kaplan–Meier curves and time-to-event summaries were constructed to examine the long-term incidence of clinical and safety end points. Univariable and multivariable Cox proportional hazard regression models were used to compare time-dependent dichotomous events among groups. Missing values were not imputed. All statistical analyses were performed with the SAS software, version 9.1 or higher (SAS Institute, Cary, NC). A P-value <0.05 was considered significant. All tests were two sided.

RESULTS

Registry Sample

The e-SELECT registry comprised 15,147 patients who fulfilled the inclusion and exclusion criteria specified in the protocol. Follow-up data were available in 14,905 patients at 30 days, 14,430 at 6 months, and 13,693 at 1 year, representing 99%, 96%, and 92% of survivors, respectively. In this analysis, 10,506 (70%) patients with 13,833 lesions were nondiabetics (ND), whereas 4,577 (30%) patients with 6,091 lesions had DM. Within the DM group, 1,238 (9%) patients with

TABLE II. Lesion and Procedure Characteristics of Insulin-Treated Diabetics, Non–Insulin-Treated Diabetics and Nondiabetics

	Diabetics			
	Insulin-treated ($n = 1,238$ patients; 1,606 lesions)	Non–insulin-treated ($n = 3,339$ patients; 4,385 lesions)	Nondiabetics ($n = 10,506$ patients; 13,833 lesions)	P*
Reference vessel diameter, mm[a]	2.85 ± 0.45	2.89 ± 0.47	2.93 ± 0.45	<0.001
Preprocedural percent stenosis[a]	84.05 ± 11.28	84.13 ± 12.30	84.70 ± 12.46	0.002
Lesion length, mm[a]	20.53 ± 11.39	19.94 ± 11.25	20.29 ± 11.72	ns
Lesion subsets				
Restenotic[b]	194 (12.0)	500 (11.4)	1,618 (11.9)	ns
In-stent restenosis[b]	179 (11.1)	469 (10.7)	1,531 (11.2)	ns
Length ≥ 30 mm	161 (13.2)	428 (13.0)	1,422 (13.7)	ns
Bifurcation[b]	207 (12.9)	582 (13.3)	2,039 (15.0)	<0.001
Chronic total occlusion[b]	51 (3.2)	114 (2.6)	452 (3.3)	0.04
Reference vessel diameter < 2.25 mm	60 (4.9)	163 (4.9)	361 (3.5)	<0.001
Ostial	203 (12.6)	516 (11.8)	1,753 (12.9)	ns
Moderately or severely calcified[b]	447 (30.0)	988 (24.7)	2,766 (22.6)	<0.001
Procedural characteristics				
Numbers per patient				
Vessels treated	1.18 ± 0.42	1.19 ± 0.42	1.17 ± 0.42	0.07
Lesions treated	1.32 ± 0.62	1.34 ± 0.61	1.32 ± 0.62	ns
Stents implanted	1.54 ± 0.88	1.56 ± 0.84	1.55 ± 0.87	ns
Overlapping stents	161 (13.0)	479 (14.3)	1,576 (15.0)	ns
Total stent length, mm				
Per lesion	25.5 ± 13.1	25.0 ± 13.0	25.4 ± 13.3	ns
Per patient	33.4 ± 21.7	33.3 ± 20.5	33.5 ± 21.0	ns
Direct stenting	550 (34.2)	1,509 (34.4)	4,937 (36.2)	0.01
Post-dilatation	606 (33.7)	1,718 (34.5)	5,720 (36.9)	<0.001
Maximal pressure, atm	17.6 ± 4.3	17.2 ± 4.2	17.0 ± 4.3	<0.001
Intravascular ultrasound imaging	44 (2.8)	132 (3.1)	537 (4.0)	<0.001
Antithrombotic regimen				
Preprocedural				
Aspirin	1,060 (87.4)	2,867 (87.3)	8,796 (85.1)	<0.001
Clopidogrel	766 (63.1)	1,938 (59.1)	6,253 (60.5)	ns
Ticlopidine	23 (1.9)	68 (2.1)	190 (1.8)	ns
Intraprocedural				
Glycoprotein IIb/IIIa inhibitor	204 (16.7)	497 (15.0)	1,652 (15.8)	ns
Bivalirudin	40 (3.3)	87 (2.6)	346 (3.3)	ns
Unfractionated/low-molecular-weight heparin	1,108 (90.7)	2,908 (87.7)	9,179 (87.9)	ns

Values are mean ± SD, or number (%) of observations.
[a]Visual estimate.
[b]The denominator is the group-specific number of lesions.
*All diabetics vs. nondiabetics.

1,633 lesions were insulin-treated diabetics (ITD). In the ITD subgroup, 244 (20%) patients were classified as type 1 DM, but the great majority presented a diagnosis of type 2 DM. The clinical characteristics of the three groups are shown in Table I. The DM group was characterized by fewer males, but a higher prevalence of obesity, other major coronary risk factors, comorbidities, and triple-vessel coronary artery disease compared with ND patients. A greater proportion of diabetic patients had a Charlson index score ≥ 3.

Lesion and Procedural Characteristics

The lesion and procedural characteristics of the three patient groups are shown in Table II. Target vessels in diabetics were smaller and were more likely to be moderately to heavily calcified, but less likely to have bifurcation involvement. Albeit statistically significant, the differences in reference vessel diameter and preprocedural percent vessel stenosis between diabetics and ND were small.

Diabetic patients were less likely to undergo direct stenting and postdilation; however, they were treated with higher maximal balloon dilation pressures. They also were less likely to undergo intravascular ultrasound assessment.

Antithrombotic and Antiplatelet Therapy

Table III shows the number of patients treated with thienopyridine, aspirin, or both at 1, 6, and 12 months. At 30-day follow-up, 97.6% of all DM patients were

TABLE III. Antithrombotic Regimen Compliance in Nondiabetics and the Two Diabetic Subgroups at 30, 180, and 360 Days of Follow-up

	Diabetics			
Antiplatelet therapy	Insulin-treated	Non–insulin-treated	Nondiabetics	*P**
30 days	*n* = 1,168	*n* = 3,168	*n* = 10,506	
Dual	1,138 (97.4)	3,093 (97.6)	9,822 (98.2)	0.02
Single	20 (1.7)	58 (1.8)	152 (1.5)	ns
None	8 (0.7)	7 (0.2)	14 (0.1)	0.02
180 days	*n* = 1,110	*n* = 3,055	*n* = 9,634	
Dual	1,047 (94.3)	2,890 (94.6)	9,123 (94.7)	ns
Single	55 (5.0)	146 (4.8)	457 (4.7)	ns
None	7 (0.6)	17 (0.6)	51 (0.5)	ns
360 days	*n* = 1,072	*n* = 2,974	*n* = 9,479	
Dual	853 (79.6)	2,425 (81.5)	7,460 (78.7)	0.002
Single	199 (18.6)	510 (17.1)	1,906 (20.1)	<0.001
None	19 (1.8)	35 (1.2)	110 (1.2)	ns

Values are number (%) of observations. Of the patients treated with a thienopyridine, 98.6% received clopidogrel and 1.4% received ticlopidine.
*All diabetics vs. nondiabetics.

TABLE IV. Cumulative Rates of Adverse Clinical Events at 1-Year Follow-up

	Diabetics			
	Insulin-treated (*n* = 1,238 patients)	Non–insulin-treated (*n* = 3,339 patients)	Nondiabetics (n = 10,506 patients)	*P**
Deaths				
From all causes	54 (4.8)	62 (2.0)	120 (1.2)	<0.001
Cardiac	41 (3.7)	40 (1.3)	55 (0.6)	<0.001
Myocardial infarction	54 (4.9)	57 (1.9)	153 (1.6)	<0.001
Q-wave	8 (0.7)	10 (0.3)	39 (0.4)	0.8
Non-Q-wave	45 (4.1)	48 (1.6)	115 (1.2)	<0.001
TLR	51 (4.7)	79 (2.6)	179 (1.9)	<0.001
PCI	45 (4.1)	73 (2.4)	162 (1.7)	<0.001
CABG	6 (0.6)	9 (0.3)	22 (0.2)	0.2
MACE	120 (10.6)	167 (5.5)	384 (4.0)	<0.001
Stent thrombosis				
0–30 days	22 (1.8)	25 (0.8)	40 (0.4)	<0.001
31-360 days	15 (1.4)	8 (0.3)	25 (0.3)	0.01
Total	37 (3.4)	33 (1.1)	65 (0.7)	<0.001
Major bleeding				
0–30 days	5 (0.4)	15 (0.5)	37 (0.4)	0.5
31-360 days	10 (1.0)	18 (0.6)	46 (0.5)	0.1
Total	15 (1.4)	33 (1.1)	83 (0.9)	0.1

Values are number (%) of observations.
*All diabetics vs. nondiabetics.
PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

treated with DAPT (clopidogrel or ticlopidine + aspirin), vs. 98.2% of ND ($P = 0.02$). Reasons for 30-day interruption of DAPT included bleeding, switching to antagonist of vitamin-K, allergy or intolerance, and emergent surgery. At 1 year, 81% of all diabetic patients received DAPT vs. 78.7% of ND ($P = 0.002$).

Stent Thrombosis, Major Bleeding, and Other MACE

The 30-, 180- and 360-day rates of MACE are presented in Table IV. Multivariable prediction analysis for MACE is reported in Table I (Supporting Information Appendix). Fig. 1A shows the cumulative incidence of ST in ITD, non–insulin-treated diabetics (NITD), and in ND. A considerably higher incidence of definite and probable ST was observed in ITD vs. the two other groups, and, at 12 months, the difference was statistically significant ($P < 0.001$) even after adjusting for baseline differences among groups (Table V). In contrast, the 1-year cumulative ST rates in the NITD subgroup and ND were similarly very low. The relationship between DAPT compliance and the incidence of early and late definite and probable ST in

diabetics and ND is shown in Fig. 2. The great majority of ST occurred during DAPT treatment in all groups (Fig. 2). In ITD fully compliant with DAPT, we observed a sixfold higher risk of ST compared with ND throughout the first year. Similarly, NITD demonstrated a higher risk of ST during the first 30 days compared with ND (0.7% vs. 0.3%, $P = 0.003$), but, beyond the first month, no significant difference in ST risk was observed between these two groups. The risk of ST after discontinuing one or both antiplatelet agents within 30 days after the index procedure was high for both diabetics and ND (3.4% and 5.3%, respectively), as shown in Table VI. The risk of ST in patients deviating from DAPT decreased rapidly beyond the first month, with an ST rate equivalent to that observed in patients fully compliant with DAPT. As seen in Table VII, ST was, to a higher degree, associated with MI in ND compared with ITD and NITD (77%, 65%, and 51%, respectively). However, ST was more often associated with fatal outcomes in ITD and NITD compared with ND (43%, 42%, and 25%, respectively).

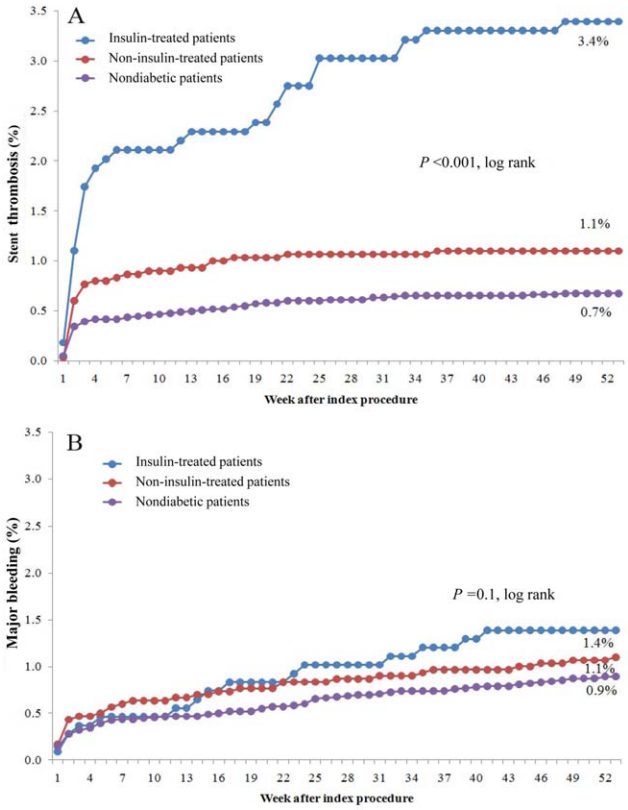

Fig. 1. Kaplan–Meier curves showing cumulative incidence of (A) stent thrombosis and (B) major bleeding complications up to 1 year in insulin-treated diabetics, non–insulin-treated diabetics and nondiabetic patients.

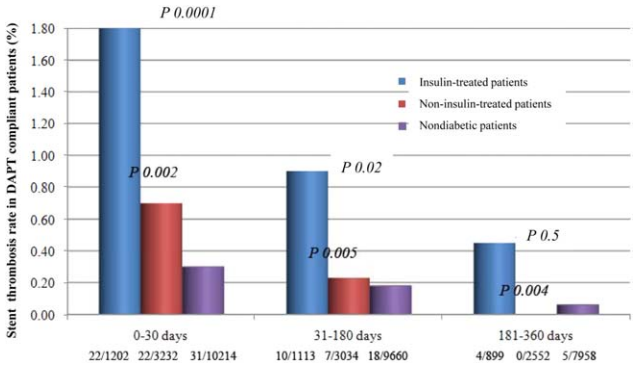

Fig. 2. Early and late stent thrombosis rates in insulin-treated diabetics, non–insulin-treated diabetics, and nondiabetic patients compliant with dual antiplatelet therapy.

TABLE V. Multivariable Predictor Analysis for Index PCI-Related ARC Stent Thrombosis[a] Within 0–360 Days

Variable	Coefficient	Standard error	Hazard ratio (95% CI)	*P*-value
Charlson comorbidity index	0.29	0.05	1.3 (1.2–1.5)	<0.001
Previous CABG	0.99	0.24	2.7 (1.7–4.3)	<0.001
ITDM	0.97	0.26	2.6 (1.6–4.4)	<0.001
Multivessel disease (two- or three-vessel disease or significant LMS)	0.60	0.23	1.8 (1.2–2.9)	0.010
ACS	0.55	0.22	1.7 (1.1–2.7)	0.014
Preprocedure Hb (by 10 g/L decrement)	0.12	0.05	1.1 (1.0–1.2)	0.015
Platelet function tested	0.61	0.26	1.8 (1.1–3.1)	0.021
Any deviation from continuous DAPT (up to 1 month FU visit)	0.77	0.37	2.2 (1.0–4.5)	0.040
Maximal lesion length (by 10 mm increment[b])	0.14	0.07	1.1 (1.0–1.3)	0.040
Diabetes with retinopathy, neuropathy, or nephropathy	−0.70	0.37	0.5 (0.2–1.0)	0.06
History of hyperlipidemia	−0.33	0.21	0.7 (0.5–1.1)	0.12
AMI (≤72 hrs) as indication for PCI	0.42	0.27	1.5 (0.9–2.6)	0.12
Age (by 10 year increment[b])	0.10	0.10	1.1 (0.9–1.3)	0.35

[a]Stent thrombosis events related to stents implanted at index procedure.
[b]Hazard ratio is per increase of 10; for Charlson comorbidity index, hazard ratio is per increase of 1.
PCI, percutaneous coronary intervention; ARC, Academic Research Consortium; CABG, coronary artery bypass grafting; ITDM, insulin-treated diabetes mellitus; LMS, left main stenosis; ACS, acute coronary syndromes; DAPT, dual antiplatelet therapy; FU, follow-up; AMI, acute myocardial infarction.

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TABLE VI. Rate of Early and Late Stent Thrombosis and Its Relationship to Antiplatelet Regimen at the Time of the Event

	0–30 days			31–180 days			181–360 days		
	DAPT	Interrupted[a]	*P*	DAPT	Interrupted[a]	*P*	DAPT	Interrupted[a]	*P*
Diabetics	1.0	3.4	0.01	0.41	0.54	0.8	0.12	0.16	0.8
Nondiabetics	0.3	5.3	<0.0001	0.18	0.24	0.8	0.06	0.06	1.0

Values are % of observations.
[a]Definitive interruption of one or both antiplatelet agents at the time of stent thrombosis.

TABLE VII. Relationships Between Definite or Probable Stent Thrombosis (ARC Definition) and Cardiac Death, Myocardial Infarction, Target Vessel Revascularization, and Major Bleeding at 1-Year Follow-up in Diabetics and Nondiabetics

	Stent thrombosis		
	Diabetics		
	Insulin-treated ($n = 37$)	Non–insulin-treated ($n = 33$)	Nondiabetics ($n = 65$)
Cardiac death	16 (43)	14 (42)	16 (25)
Myocardial infarction	24 (65)	17 (51)	50 (77)
Target vessel revascularization	27 (73)	19 (58)	45 (69)
Major bleeding	0 (0)	0 (0)	2 (3)

Values are number (%) of observations in the corresponding subgroup.
ARC, Academic Research Consortium.

As reported in Table IV and depicted in Fig. 1B, there was an overall low risk of major bleeding during follow-up, and no significant difference in the type of major bleeding events among the three groups (Fig. 1, Supporting Information Appendix). The freedom from major bleeding was not different comparing ITD (1.4%), NITD (1.1%), and ND (0.9%), with a log-rank *P*-value of 0.1. Multivariable analysis failed to prove that DM was an independent predictor of major bleeding during follow-up (Table II, Supporting Information Appendix). Moreover, none of the DM patients who experienced ST within 1 year had a major bleeding event (Table VII).

DISCUSSION

The e-SELECT registry collected longitudinal outcome data of the largest, unselected ("real-world"), consecutive cohort of patients treated with SES implantation (Cypher Select® or Cypher Select Plus®). This report summarizes pertinent performance data in the DM group, assessing differential outcome in ITD and NITD subgroups. Patients with DM presented a higher cumulative rate of MACE compared with the ND group, which was consistently higher among ITD compared with NITD. As previously reported, diabetics presented also a higher rate of acute and subacute ST compared with the ND counterpart (1.5% vs. 0.7%, $P < 0.001$), which was principally owing to ITD in patients with DM and significantly associated in each of the three patient groups with premature (within 30 days) DAPT discontinuation. However, it is noteworthy that DAPT compliance in our study was significantly higher than that previously reported [8,9].

Clinical results after PCI with first-generation SES have been reported in many large randomized controlled trials, clinical registries, and small single-center series (Table III, Supporting Information Appendix) [10–13]. Our data confirm the safety and efficacy of PCI using first-generation SES, extending previous observations in a very large consecutive and unselected cohort of DM patients. The Drug-Eluting Stent.DEutschland (DES.DE) registry enrolled 1,526 diabetic patients undergoing PCI with either first-generation SES or paclitaxel-eluting stents at 98 sites [14]. In the SES group, 1-year mortality and MI rates were 5.8% and 4.2%, respectively, with an overall target vessel revascularization (TVR) rate of 12% [14]. Similarly to our data, ITD in the DES.DE registry had higher rates of overall death (7.4% vs. 4.6%), TVR (15.1% vs. 10.4%), and ST (6.5% vs. 4.1%) [15]. However, the overall ST rate was markedly higher than that observed in our analysis. To this regard, our data provide an important piece of evidence concerning the "real-world" risk of ST after first-generation SES implantation when DAPT compliance in daily clinical practice is high. Indeed, this risk was lower than that historically reported [16,17] but similar to what has been shown by other more recent clinical registries [13,18]. Moreover, our analysis including a large number of ITD provides strong supporting evidence regarding the interaction between insulin use and long-term

prognosis after PCI in DM. In the e-SELECT registry, in addition to higher MACE rate, ITD had a significantly shorter event-free survival from Academic Research Consortium definite ST compared with NITD, which accounts almost exclusively for the outcome difference between patients with and without DM. In the E-Five registry (Table III, Supporting Information Appendix), 12-month outcome data in the DM subgroup were reported [8]. Interestingly, that study showed that insulin therapy was not statistically associated with increased propensity for ST, even though, similarly to our study, ITD remained at increased risk of other adverse cardiovascular events. Understanding the association between insulin therapy and unfavorable PCI outcomes is challenging. In our study, as in others, ITD do present a more aggressive cardiovascular risk profile, including renal failure and other co-morbidities that may explain the increased risk of ST and other adverse events. Insulin resistance has been associated with detrimental biological processes, such as impaired vascular production of nitric oxide and increased levels of endothelin-1 and angiotensin-II [19]. However, insulin therapy *per se* may adversely affect cellular proliferation increasing in-stent restenosis risk and may play a complex role in promoting ST. Interestingly, although lesion characteristics between ITD and NITD were similar, the former experienced a higher TLR rate, which again reinforces the hypothesis of a different biological milieu in this patient population.

Bleeding complications carry an ominous prognostic implication in PCI patients [20,21]. The strong association between bleeding and unfavorable outcome is particularly relevant in acute coronary syndromes because of multiple factors, including premature DAPT discontinuation, need of transfusion, and background relationship between bleeding propensity and adverse overall cardiovascular risk profile [22–25]. In our study, the ongoing major bleeding risk during follow-up was substantially lower than that previously reported and was not significantly different among groups [26]. These results are similar to those of other recent DES registries in diabetics and do reassure regarding the ongoing bleeding risk in these patients treated with DAPT up to 1 year after PCI [4,14].

The complex interplay linking DM to unfavorable PCI results includes altered inflammatory pathways, endothelial dysfunction, aggressive thrombogenesis, and monocyte activation, leading to foam cell transformation and altered smooth muscle cell migration [27,28]. These mechanisms not only are implicated in the progression of clinically significant coronary artery disease but may also jeopardize long-term PCI results [29–31]. Accordingly, concerns have been raised regarding PCI in DM patients, especially in case of multivessel disease, which prompted extensive research exploring the potential superiority of surgical revascularization [32]. Although randomized controlled trials suggested a competitive efficacy of bypass surgery over PCI in diabetics with complex multivessel disease, it is routine practice worldwide to refer these patients to the catheterization laboratory in a significant proportion of cases [33]. The advent of the DES era led to improved results among diabetics, thereby narrowing the outcome gap with surgical revascularization [34,35]. However, recent randomized, controlled trials, such as the Coronary Artery Revascularization in Diabetes (CARDia) trial, the Synergy between PCI with Taxus and cardiac surgery (SYNTAX) trial, and the Future Revascularization Evaluation in patients with Diabetes Mellitus (FREEDOM) trial, did demonstrate long-term superiority of coronary bypass over PCI, mainly driven by a lower TLR rate, particularly in patients with highly complex lesions [36–38]. One major limitation of any randomized controlled trial comparing surgery with PCI is the presence of multiple exclusion criteria that reduces the external validity of trial-related findings. For example, in the FREEDOM trial, patients with congestive heart failure (NYHA class III or IV), prior cardiac valve surgery, recent (<6 months) PCI, prior stroke, acute ST-elevation MI, and left main stenosis $>50\%$ were excluded [39]. Accordingly, our data have additive value because they are able to provide insights of PCI efficacy in a "real-world" scenario, which may help clinicians in daily clinical practice to choose differential therapeutic strategies in DM patients with coronary artery disease.

Finally, the field of PCI is rapidly evolving, and first-generation DES have been overtaken by second-generation DES, which are expected to be replaced, at least in specific subsets of patients, by third-generation devices (bioresorbable-polymer-coated or fully bioresorbable DES) [40]. However, it is noteworthy that direct comparison of a zotarolimus-eluting stent (Endeavor, Medtronic, Minneapolis, MN) with the Cypher stent in the Danish Organization for Randomized Trials with Clinical Outcome (SORT OUT) III trial (Table III, Supporting Information Appendix) showed that treatment with the Endeavor stent compared with the Cypher stent was associated with higher MACE rate, including TVR and TLR in both diabetics and ND, with a greater magnitude of differential effect in the DM group [41]. Comparing our outcome data with the E-Five Registry that enrolled all-comer PCI patients treated with the Endeavor stent [8], we can indirectly extend the SORT OUT III trial data in a real-world population, given that the overall MACE rate in the E-Five registry was consistently higher than

that observed in our population (overall mortality 4.0% vs. 2.5% and TLR rate 5.3% vs. 2.8%; Table III, Supporting Information Appendix). Recently, the Resolute zotarolimus-eluting stent (Medtronic) received the FDA labeling for DM patients on the basis of a prespecified performance goal (target vessel failure $< 14.5\%$) at 12 months in diabetics [42]. Interestingly, the prespecified target vessel failure end point (including cardiac death, vessel-related MI, and ischemia driven revascularization) was reported in 7.8% of the 878 diabetic patients [42]. In our study, a similar outcome of cardiac death, TLR, and MI occurred in 322 (7.0%) of the 4,577 DM patients. Overall, the presence of DM seems to limit the improved comparative effectiveness of second-generation DES over first-generation DES generally observed in ND. Accordingly, we believe that our data may serve as a benchmark for future revascularization strategies in DM patients with or without the need for insulin therapy.

Limitations

This study is limited by the fact that the Cypher stent has been withdrawn from the market in most countries. However, SES are still used in several centers worldwide, and our data may help designing future studies in diabetics. Because we monitored the source data collected in a random sample representing 20% of enrolled patients, underreporting of adverse events remains a potential limitation.

Patients were included only after successful SES implantation and if they did not have contraindications to prolonged DAPT. This may affect generalizability of our findings for specific patient subgroups. No information was available on efficacy of diabetic treatment, measured by HbA1c levels, and the severity of DM was estimated by insulin requirement only. Finally, follow-up was 1 year only. Thus, it is possible that the relative ST and MACE risk may have changed with a longer follow-up, particularly after DAPT discontinuation.

Intravascular ultrasound was less commonly used in DM patients compared with ND, and this may have had a role in promoting increased propensity to ST in diabetics.

Insulin requirement does not segregate type 1 and type 2 DM patients. However, in our study, the number of patients with type 1 DM was not large, making the assessment of differential outcomes in these two pathophysiologically different DM subgroups challenging. In addition, insulin requirement may serve as a clinical benchmark of a more aggressive metabolic derangement, and it is useful in clinical practice to stratify diabetic patients.

CONCLUSIONS

Treatment with SES in the e-SELECT registry was associated with an acceptably low rate of MACE in a large cohort of unselected real-world patients with DM. However, ST was significantly more frequent as compared with ND, and this difference was mainly driven by ITD.

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