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The Sirolimus-Eluting Cypher Select Coronary Stent for the Treatment of Bare-Metal and Drug-Eluting Stent Restenosis

Insights From the e-SELECT (Multicenter Post-Market Surveillance) Registry

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Objectives This study sought to compare the 1-year safety and efficacy of Cypher Select or Cypher Select Plus (Cordis Corporation, Bridgewater, New Jersey) sirolimus-eluting stents (SES) with the treatment of bare-metal stents (BMS) and drug-eluting stent (DES) in-stent restenosis (ISR) in nonselected, real-world patients.

Background There is paucity of consistent data on DES for the treatment of ISR, especially, DES ISR.

Methods The e-SELECT (Multicenter Post-Market Surveillance) registry is a Web-based, multicenter and international registry encompassing virtually all subsets of patients and lesions treated with at least 1 SES during the period from 2006 to 2008. We enrolled in this pre-specified subanalysis all patients with at least 1 clinically relevant BMS or DES ISR treated with SES. Primary endpoint was major adverse cardiac events and stent thrombosis rate at 1 year.

Results Of 15,147 patients enrolled, 1,590 (10.5%) presented at least 1 ISR (BMS group, n = 1,235, DES group, n = 355). Patients with DES ISR had higher incidence of diabetes (39.4% vs. 26.9%, $p < 0.001$), renal insufficiency (5.8% vs. 2.3%, $p = 0.003$), and prior coronary artery bypass graft (20.5% vs. 11.8%, $p < 0.001$). At 1 year, death (1.4% for BMS vs. 2.1% for DES, $p = 0.3$) and myocardial infarction (2.4% for BMS and 3.3% for DES, $p = 0.3$) rates were similar, whereas ischemia-driven target lesion revascularization and definite/probable late stent thrombosis were higher in patients with DES ISR (6.9% vs. 3.1%, $p = 0.003$, and 1.8% vs. 0.5%, $p = 0.04$, respectively).

Conclusions Use of SES for either BMS or DES ISR treatment is safe and associated with low target lesion revascularization recurrence and no apparent safety concern. (J Am Coll Cardiol Intv 2012;5:64–71) © 2012 by the American College of Cardiology Foundation

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Excessive neointimal growth leading to in-stent restenosis (ISR) has been the major drawback of percutaneous coronary intervention, occurring in up to 25% to 30% of the cases treated with bare-metal stents (BMS).

From balloon angioplasty and atherectomy to intravascular brachytherapy (IVB), many alternative strategies were investigated as treatment options in this challenging scenario (1–4). However, none of them achieved the expected efficacy and safety profile and, in some cases, the logistical demands precluded the worldwide acceptance of the strategy.

With their efficacy and superiority over BMS demonstrated in a variety of complex clinical and angiographic settings (5–7), drug-eluting stents (DES) were rapidly incorporated into clinical practice and became the treatment of choice for difficult situations, including BMS ISR (8–10).

Although infrequent, DES ISR still occurs, and the best approach to treat it is yet to be defined. Using data from the e-SELECT (Multicenter Post-Market Surveillance) registry, a large, prospective and observational registry of patients who underwent implantation of sirolimus-eluting stents (SES), we aimed to determine 1-year efficacy and safety of Cypher Select or Cypher Select Plus (Cordis Corporation, Bridgewater, New Jersey) SES for the treatment of previous BMS and DES ISR in complex patients treated in routine daily practice.

Methods

The present study represents a pre-specified subanalysis of the prospective, international e-SELECT registry. Details of this registry have been published (11) elsewhere. In brief, e-SELECT was conducted at 320 medical centers (listed in the Online Appendix) in 56 countries where SES were approved for commercial use. Baseline data were collected between May 2006 and April 2008 in consecutive and eligible patients who underwent implantation of ≥1 Cypher Select or Cypher Select Plus SES according to standard clinical practice and procedural techniques. It is important to note that both SES have the same polymer and amount of antiproliferative drug (with identical kinetic release profile). Cypher Select or Cypher Select Plus only differs in the platform design, because there were slight modifications in the latest one to enhance flexibility and deliverability.

The protocol specified very few inclusion or exclusion criteria. Lesions could be pre-treated with any technique or device, such as balloon angioplasty, cutting balloon, or atherectomy, but implantation of SES in each target lesion during the index procedure was mandatory. All post-operative medical management, including antithrombotic therapy, was prescribed according to usual local practice. The protocol was approved by the ethics committee of each participating center and the patients granted their consent to participate in the registry. Patients for whom the collection of dependable follow-up information was unlikely and those who received a stent other than a SES during the index procedure were excluded.

For the present study, we included all patients with at least 1 BMS or DES ISR treated with percutaneous coronary intervention and SES deployment. We defined ISR as ≥50% angiographic stenosis within or 5 mm proximal and distal to the stent.

Data collection and management. The data collected by the e-SELECT registry include demographic information, cardiovascular history, comorbidity, lesion and procedure characteristics, and antithrombotic regimens. Patients were followed at 30, 180, and 360 days by telephone communication, office visit, or by contacts with primary physicians or referring cardiologists.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
HR = hazard ratio
ISR = in-stent restenosis
IVB = intravascular brachytherapy
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TLR = target lesion revascularization

The data were collected electronically at each participating center and transferred to an independent data management organization (KIKA Medical, Nancy, France). After verification of their consistency, the data were analyzed by an independent clinical research organization (Cardialysis, Rotterdam, the Netherlands). The accuracy of data collection was monitored by an independent organization (Covance, Princeton, New Jersey) in 20% of the overall sample, at 100 centers selected by a stratification scheme based on patient enrollment, region of the world, and rate of data outliers. The consistency and accuracy of data contained in the source documentation versus that entered in the electronic database were verified using an anonymous procedure to preserve confidentiality. The data were "consistent" when present in both the source documents and in the electronic database and "accurate" when the electronic database fully matched the data entered in the source documents. Using these definitions, overall

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data consistency was 99%. The accuracy of baseline data was 96%, and that of adverse events recorded during follow-up was 93.2%.

Study endpoints. The primary objective of this subanalysis was the comparison of major adverse cardiac events (MACE) and stent thrombosis (ST) at 1-year clinical follow-up of patients with BMS or DES ISR treated with a SES.

MACE were defined as cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). All deaths were considered cardiac unless a noncardiac origin could be clearly established by clinical and/or pathological study. The diagnosis of MI was based on either the development of new pathological Q waves in ≥2 contiguous electrocardiogram leads and/or post-procedure elevation of creatine kinase-myocardial band isoenzyme >3 times the upper normal limit during index hospitalization, or cardiac enzyme elevation >2 times the upper normal limit thereafter. TLR was considered clinically driven when it was prompted by symptoms and/or signs of ischemia.

Stent thrombosis was classified as definite, probable, and possible according to definitions proposed by the Academic Research Consortium and was stratified as acute (<24 h), subacute (24 h to 30 days), and late (1 to 12 months).

Procedural success was defined as angiographic success plus absence of MACE during hospitalization.

Study organization and supervision. A steering committee planned the analysis, presentations, and publications of registry data. The algorithms used to classify clinical events and the criteria used for the adjudications of MACE 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. The committee adjudicated all MACE, deaths, ST, and MI by a systematic review of the data collection forms and by review of the source documents, electrocardiograms, and angiograms, when necessary. Routine angiographic follow-up was not part of the study protocol.

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 mean ± SD or medians and range, and compared using Student *t* test, whereas categorical variables are presented as numbers and percentages and compared using chi-square test. When the assumptions were broken, Fisher exact test was used.

Cumulative rates of adverse clinical events were calculated using event-specific adjusted denominators, so that all patients suffering an event within 360 days, or followed up for at least 330 days after the index procedure, contributed to the denominator. There was no censoring. Kaplan-Meier curves and time-to-event summaries were constructed, using the life-table method, to examine the long-term incidence of clinical and safety endpoints. Predictors of major clinical safety endpoints were identified by univariate and multivariate analyses using Cox proportional hazards model. For each outcome endpoint, baseline covariates identified by the univariate analysis ($p < 0.05$), by the proportional hazards assumption test ($p \geq 0.05$ combined with graphic assessment), and by clinical relevance were included in the multivariate model stepwise selection procedure. An entry criterion probability value of 0.10 and a stay criterion of 0.05 were used and baseline covariates with >15% missing values were excluded from analysis. No missing value imputation was performed. All statistical analyses were performed with SAS software (version 9.1 or higher, SAS Institute, Cary, North Carolina).

Results

The e-SELECT database registered 15,400 patients, 253 of whom were deregistered after online data queries and on-site monitoring of source data, resulting in a sample of 15,147 patients who were compliant with the inclusion/exclusion criteria specified in the protocol. Among them, 1,590 (10.5%) patients had 1 or more ISR as the index procedure target lesions. These patients were divided in 2 groups according to the type of stent that resulted in the restenotic lesion (BMS group, n = 1,235; DES group, n = 355).

Patients with DES ISR had significantly more comorbidity, as shown by a higher incidence of diabetes (39.4% vs. 26.9%, $p < 0.001$), renal insufficiency (5.8% vs. 2.3%, $p = 0.003$), and Charlson index ≥3 (20.0% vs. 13.1%, $p = 0.002$). Of note, acute coronary syndrome was frequently the initial manifestation of ISR for both BMS (43.5%) and DES (44.2%, $p = 0.81$), with more than 10% of ST-segment elevation MI in each cohort (10.2% in BMS ISR vs. 13% in DES ISR, $p = 0.15$). Table 1 contains the detailed baseline clinical characteristics.

Overall, the lesion per patient rate was 1.11, with significant difference between groups (1.07 lesion/patient in the DES cohort vs. 1.12 lesion/patient in the BMS population, $p = 0.011$). A diffuse restenosis pattern (≥20 mm) was more frequent in the BMS group than in the DES group (55.7% vs. 42.2%, $p < 0.001$). Mean estimated lesion length was significantly longer in the BMS group (22.5 ± 12.4 vs. 19.3 ± 11.1, $p < 0.001$) but with a stented length/lesion length ratio similar between groups (1.40 in the BMS vs. 1.36 in the DES, $p = 0.37$). The estimated reference vessel diameter was also equivalent between groups (2.99 ± 0.42 mm in the DES cohort vs. 3.00 ± 0.43 mm in the BMS group, $p = 0.71$). Detailed procedure characteristics are displayed in Table 2.

A total of 88.2% (1,089 of 1,235 of the patients from the BMS ISR group) and 91.3% (324 of 355) from the DES ISR cohort completed the 12-month clinical follow-up ($p = 0.1$). At 1 year (Table 3), the incidence of death (1.4% for BMS vs. 2.1% for DES, $p = 0.3$) and MI (2.4% for BMS and 3.3% for DES, $p = 0.3$) did not significantly differ between groups. However, ischemia-driven TLR was higher among patients

Table 1. Baseline Clinical Characteristics

Variable	BMS-ISR (n = 1,235)	DES-ISR (n = 355)	p Value
Age			0.46
Mean ± SD (N)	63.20 ± 10.77 (1,235)	63.67 ± 10.50 (355)	
Median (min, max)	63.0 (28.0, 90.0)	64.0 (32.0, 85.0)	
Male	73.3 (905/1,235)	70.4 (250/355)	0.31
Diabetes mellitus	26.9 (332/1,233)	39.4 (140/355)	<0.001
Insulin-treated	6.3 (78/1,235)	15.5 (55/355)	<0.001
Hypertension	76.9 (948/1,233)	71.3 (253/355)	0.035
Hyperlipidemia	81.1 (1,000/1,233)	79.8 (283/355)	0.59
Smoking	54.1 (667/1,233)	54.1 (192/355)	1.00
Renal insufficiency, Cr >177 μmol/l	2.3 (25/1,091)	5.8 (19/326)	0.003
Body mass index ≥30 kg/m^2	24.9 (308/1,233)	28.2 (99/351)	0.24
Charlson comorbidity index ≥3	13.1 (162/1,233)	20.0 (71/355)	0.002
Prior CABG	11.8 (146/1,233)	20.5 (73/355)	<0.001
Clinical presentation of unstable angina	33.3 (411/1,235)	31.2 (111/355)	0.52
Clinical presentation of MI	10.2 (126/1,235)	13.0 (46/355)	0.15
Left ventricular function <30%	2.3 (17/732)	6.4 (11/173)	0.012
Acute coronary syndrome	43.5 (537/1,235)	44.2 (157/355)	0.81

Values are % (n/N) unless otherwise noted.

BMS = bare-metal stent(s); CABG = coronary artery bypass graft; Cr = serum creatinine; DES = drug-eluting stent(s); ISR = in-stent restenosis; MI = myocardial infarction.

with previous DES ISR (6.9% vs. 3.1%, p = 0.003). Although there was a trend toward an overall higher rate of definite/probable ST among patients with DES ISR, this was not statistically significant (2.4 vs. 1.2, p = 0. 12) and was entirely due to a significantly higher occurrence of late ST among these subjects (1.8% vs. 0.5%, p = 0.04) (Table 4).

Figures 1 and 2 show the Kaplan-Meier survival curve free of MACE, death, MI, and TLR of the 3 treatment populations in comparison included in the e-SELECT registry. It is clear that patients with previous BMS ISR treated with SES have outcomes very similar to a de novo lesion population, whereas patients treated for DES ISR had less favorable outcomes with significantly worse survival curve free of MACE (Fig. 1) mainly because of a higher incidence of MI and TLR (Figs. 2B and 2C).

Notably, procedure success and 1-year clinical outcomes were equivalent for patients successfully treated with either Cypher Select or Cypher Select Plus SES.

It is important to notice that adherence to dual antiplatelet regimen was relatively high in both groups. At 6 months, 94.6% and 94.8% of patients in the DES ISR and BMS ISR cohorts were taking the dual antiplatelet regimen (p = 0.89), whereas at 1 year, 81.5% of the individuals in the DES ISR group and 83.6% in the BMS cohort (p = 0.4) were taking both medicines.

The independent predictors of MACE following the use of SES for the treatment of BMS ISR were diabetes mellitus (hazard ratio [HR]: 2.7 [interquartile range (IQR): 1.6, 4.4], p < 0.001), Charlson comorbidity index (HR: 1.1 [IQR: 1.0, 1.1], p < 0.001), age (by 10-year increment, HR: 1.5 [IQR: 1.1, 1.9], p = 0.005), previous coronary artery bypass graft (HR: 2.2 [IQR: 1.3, 4.0], p = 0.006), American College of Cardiology/American Heart Association lesion morphology class B2 or C (HR: 2.5 [IQR: 1.3, 4.7], p = 0.006), and multivessel disease (2- or 3-vessel disease, HR: 2.0 [IQR: 1.2, 3.3], p = 0.009). Independent predictors of TLR in the same cohort were diabetes mellitus (HR: 4.6 [IQR: 2.3, 9.3], p < 0.001), bypass graft lesion (HR: 5.1 [IQR: 2.0, 13.2], p < 0.001), any cancer (solid/metastatic/lymphoma/leukemia, HR: 15.7 [IQR: 2.0, 121.4], p = 0.008), multivessel disease (2- or 3-vessel disease, HR: 2.2 [IQR: 1.1, 4.5], p = 0.021).

In the DES ISR cohort, the independent predictors of MACE were diabetes mellitus in advanced stage (with retinopathy, neuropathy, or nephropathy, HR: 6.8 [IQR: 3.1, 15.2], p < 0.001), post-procedure residual stenosis >20% (HR: 11.9 [IQR: 2.7, 52.2], p = 0.001), and bifurcation lesion treated with ≥2 stents (HR: 13.0 [IQR: 1.7, 101.5], p = 0.015). Independent predictors of TLR in the same cohort were post-procedure diameter stenosis >20% (HR: 14.2 [IQR: 3.2, 63.7], p < 0.001), diabetes mellitus in advanced stage (HR: 5.4 [IQR: 2.0, 14.8], p = 0.001), bifurcation lesion treated with ≥2 stents (HR: 21.3 [IQR: 2.7, 169.2], p = 0.004), and the total number of lesions treated (HR: 4.6 [IQR: 1.5, 14.5], p = 0.009).

For the overall cohort (combining BMS and DES together), similar approaches were performed. For the multivariate analysis, the treatment groups (BMS vs. DES) were forced in the model and stepwise procedures were performed using selected covariates from univariate step. The independent predictors for MACE were

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Table 2. Procedure Characteristics

Variable	BMS-ISR (N = 1,235 Patients, N = 1,380 Lesions, N = 1,660 Stents)	DES-ISR (N = 355 Patients, N = 380 Lesions, N = 442 Stents)	p Value
Number of lesions treated	1,380	380	0.09
Patients with multiple lesions	10.0 (123/1,235)	7.0 (25/355)	
Type of restenosis			
Focal, <10 mm	5.3 (74/1,375)	9.2 (35/380)	0.008
Tubular, ≥10 to <20 mm	38.8 (534/1,375)	48.7 (185/380)	<0.001
Diffuse, ≥20 mm	55.7 (767/1,375)	42.1 (160/380)	<0.001
Type of DES with restenosis, %			
Endeavor	NA	15	NA
Taxus	NA	33.8	NA
Cypher	NA	26.4	NA
Xience V/Promus	NA	1.1	NA
Others	NA	23.7	NA
Lesion length, mm			<0.001
Mean ± SD (N)	22.51 ± 12.40 (1,375)	19.31 ± 11.11 (380)	
Median (min, max)	20.0 (2.0, 100.0)	16.0 (4.0, 90.0)	
Reference vessel diameter, mm			0.71
Mean ± SD (N)	3.00 ± 0.43 (1,380)	2.99 ± 0.42 (380)	
Median (min, max)	3.0 (1.5, 10.0)	3.0 (2.0, 4.2)	
Lesion located in an SVG	2.5 (35/1,380)	5.8 (22/380)	0.003
Stents/patient			0.008
Mean ± SD (N)	1.34 ± 0.65 (1,235)	1.25 ± 0.53 (355)	
Median (min, max)	1.0 (1.0, 5.0)	1.0 (1.0, 5.0)	
Pre-dilation	67.1 (926/1,380)	66.6 (253/380)	0.85
Post-dilation	38.7 (621/1,604)	48.4 (207/428)	<0.001
Stented length/lesion length per lesion, mm			0.37
Mean ± SD (N)	1.40 ± 0.75 (1,326)	1.36 ± 0.50 (368)	
Median (min, max)	1.2 (0.1, 12.5)	1.2 (0.3, 5.4)	
Bifurcation	16.2 (98/602)	9.3 (19/203)	0.015

Values are % (n/N) unless otherwise noted. Cypher stent is a product of Cordis Corporation (Bridgewater, New Jersey). Endeavor stent is a product of Medtronic, Inc. (Minneapolis, Minnesota). Promus and Taxus stents are products of Boston Scientific (Natick, Massachusetts). Xience V is a product of Abbott Vascular (Abbott Park, Illinois).

NA = nonapplicable; SVG = saphenous vein graft; other abbreviations as in Table 1.

moderate-to-severe renal disease, diabetes mellitus, post-procedure diameter stenosis (residual stenosis) >20%, multivessel disease (2 or 3 vessels), pre-dilation, and previous coronary artery bypass graft. When controlling these covariates, the HR of DES versus BMS were 1.1 [IQR: 0.7, 1.8], and p = 0.605. The independent predictors for TLR were diabetes mellitus, ostial location, and pre-dilation. When controlling these covariates, the HR of DES versus BMS was 2.0 [IQR: 1.2, 3.5], with a significant p value of 0.010.

Table 3. In-Hospital and Long-Term MACE

Event	BMS-ISR (n = 1,235)	DES-ISR (n = 355)	p Value
1-year MACE	5.7 (63/1,115)	9.5 (32/336)	0.016
Death	1.4 (15/1,111)	2.1 (7/334)	0.300
MI	2.4 (26/1,100)	3.3 (11/331)	0.300
Ischemia-driven TLR	3.1 (34/1,100)	6.9 (23/331)	0.003

Values are % (n/N).

MACE = major adverse cardiac event(s); TLR = target lesion revascularization; other abbreviations as in Table 1.

Table 4. Definite/Probable ST Distribution According to Different Time Points

Event	BMS-ISR (n = 1,235)	DES-ISR (n = 355)	p Value
Definite/probable ST	1.2 (13/1,100)	2.4 (8/331)	0.12
Early, 0 to 30 days	0.6 (7/1,229)	0.6 (2/352)	1.00
Acute, 0 to 1 day	0.1 (1/1,233)	0.0 (0/355)	1.00
Subacute, 2 to 30 days	0.5 (6/1,229)	0.6 (2/352)	1.00
Late, 31 to 360 days	0.5 (6/1,097)	1.8 (6/330)	0.04

Values are % (n/N).

ST = stent thrombosis; other abbreviations as in Table 1.

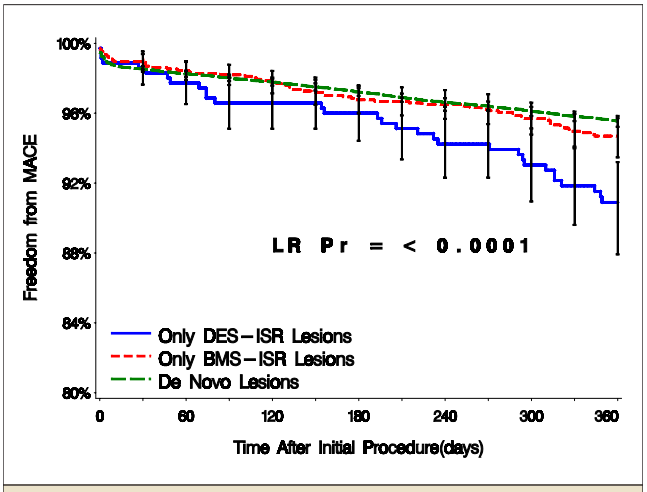

Figure 1. Kaplan-Meier Survival-Free Curve of MACE for Patients With BMS and DES ISR Compared With Those With De Novo Lesion Enrolled in the Registry

Patients with initial presentation of drug-eluting stent (DES) in-stent restenosis (ISR) had worse 1-year outcomes than did those with de novo or bare-metal ISR ($p < 0.001$ for both comparisons). BMS = bare-metal stent(s); LR = logistic regression; MACE = major adverse cardiac event(s); Pr = p value for the regression model.

The relatively low number of stent thrombosis precluded the assessment of independent predictors of this event.

Discussion

The main findings of this subanalysis of the e-SELECT registry are that percutaneous treatment of BMS and DES ISR with the deployment of SES in routine clinical practice represents a simple, feasible, and safe approach with high rate of acute success and relatively low incidence of serious adverse events up to 1-year of clinical follow-up. Even so, ISR recurrence among patients with previous DES ISR remains elevated (~7%), meaning that alternative treatment strategies might still be evaluated.

Whereas BMS eliminated acute recoil, abrupt vessel closure, and chronic negative remodeling, the main mechanisms behind balloon angioplasty failure, the deployment of these metal devices was associated with the occurrence of exacerbated local "healing" response resulting in an abnormal neointimal tissue proliferation within the stent and recurrence of ischemic symptoms requiring additional revascularization procedures (12).

Before the introduction of DES, wide varieties of percutaneous approaches were tested to treat BMS ISR. Among them, IVB was the most successful strategy, with pivotal clinical trials showing promising midterm results (13–15). However, the widespread use of IVB was limited due to logistic reasons (mainly the need for complex equipment and a large multispecialty team), radiation safety concerns, evidence of late loss of clinical efficacy (the "late catch-up" phenomenon) (16), and safety issues (late stent thrombosis) (17).

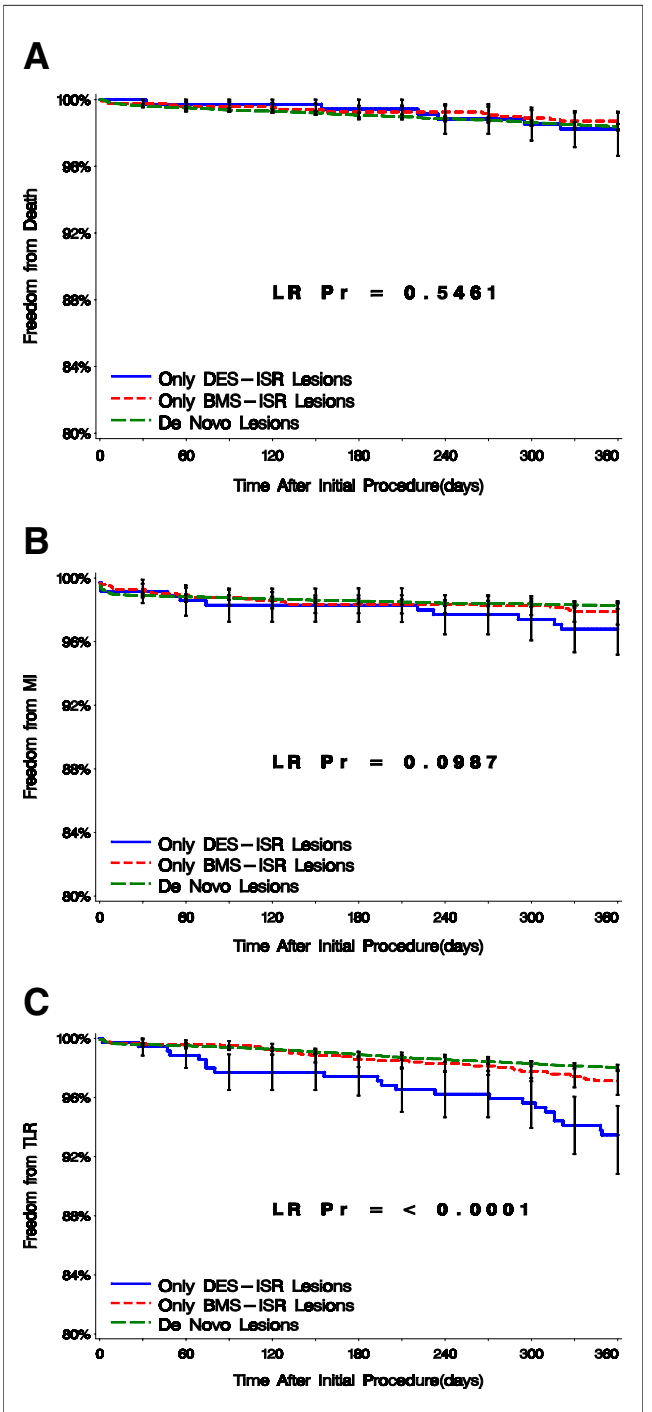

Figure 2. Kaplan-Meier Survival-Free Curves of Death, MI, and TLR for Patients With De Novo Lesions, BMS-ISR, and DES-ISR

(A) Death, **(B)** myocardial infarction (MI), and **(C)** target lesion revascularization (TLR). Treatment of DES ISR resulted in higher TLR rates at 1 year as compared to those with de novo or bare-metal ISR ($p < 0.001$ for both comparisons). Abbreviations as in Figure 1.

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The advent of DES and the demonstration of their marked suppression of neointimal formation resulting in very low rates of restenosis in a variety of complex clinical and angiographic scenarios made these novel devices a relatively simple and attractive option to treat BMS ISR. Consequently, the use of DES was tested against and showed superiority over balloon angioplasty alone (18), implant of another BMS (19), and intravascular brachytherapy (20,21). Of note, the SISR (Sirolimus-Eluting Stent vs. Brachytherapy in Patients With Bare Metal In-Stent Restenosis) trial randomized 384 patients with BMS ISR to either DES (Cypher) or IVB (20). At the end of 9 months, target vessel failure was observed in 21.6% of the patients treated with IVB and 12.4% in those treated with DES ($p = 0.02$). Similarly, the TAXUS V trial compared 196 patients with BMS ISR treated with the Taxus stent (Boston Scientific, Natick, Massachusetts) to 201 patients treated with IVB (21). At 9 months, patients allocated to the Taxus arm experienced a reduction of 60% in the need for target vessel revascularization ($p < 0.05$). Because of these studies, DES implantation became the first choice of treatment for BMS ISR.

If the question about the best way to treat BMS ISR was thus adequately answered, the same could not be said about DES ISR. Following the growing use of DES in the most complex scenarios, DES ISR also was increasingly observed in patients. Intuitively, the deployment of another DES to treat the restenosis became an option in many centers worldwide, despite the lack of large randomized controlled trials attesting the safety and efficacy of this strategy. Lemos et al. (22) were the first to report the 9-month results of 24 patients with DES ISR treated with Cypher. They observed a recurrence of restenosis in 18.2% of the cases.

Following this pioneering report, many other series comparing different strategies were published from different centers. Abe et al. (23) published a subanalysis of the Japanese registry of Cypher (J-Cypher) where they compared the deployment of a Cypher stent versus plain balloon angioplasty for the treatment of Cypher ISR. At 2 years, patients treated with another Cypher had significantly less recurrence of ISR (23.8% vs. 37.7%, $p < 0.0001$), but 2-year mortality (10.4% in the Cypher vs. 10.8% in the plain balloon angioplasty, $p = 0.4$) and ST (0.6% for both groups) did not differ between cohorts.

In the ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis) 2 trial, Mehilli et al. (24) reported the outcomes of 450 consecutive patients with Cypher ISR randomized (1:1) to receive either a different DES type (Taxus paclitaxel-eluting stent) or the same DES. At the end of 1-year follow-up, both cohorts presented similar rates of death/MI (6.1% for Cypher vs. 5.8% for Taxus, $p = 0.86$), TLR (16.6% vs. 14.6%, $p = 0.52$), and stent thrombosis (0.4% vs. 0.4%, $p = 0.99$). Compared to both series, the present registry included a significantly larger patient population and presents the lowest rate of TLR after use of SES for the treatment of DES ISR. A possible explanation could be the absence of routine follow-up angiography in the e-SELECT registry, which reflects the current clinical practice and prevents the oculostenotic reflex, a frequent cause of unnecessary repeated procedures.

The finding of a higher late ST rate among patients with previous DES ISR might be explained by the more complex clinical and angiographic characteristics of this cohort that included a significantly higher number of patients with diabetes, longer lesions, higher Charlson comorbidity index, and renal failure. All these characteristics have been previously correlated with incremental occurrence of ST (25–28).

Although not fully satisfactory in terms of TLR recurrence, to date the deployment of another DES, in particular a SES, has been the most widely tested and most effective strategy to treat DES ISR. However, it is important to consider the mechanisms behind the failure of SES to treat a DES ISR, because the only independent predictor of TLR among these patients in the present study was a residual stenosis >20% at the end of the baseline procedure, most probably often reflecting stent underexpansion.

Based on this finding, it is imperative to stress again the importance of adequate stent implantation technique, including aggressive stent post-dilation and, when needed, intravascular ultrasound guidance, as a way to optimize acute procedure results and minimize the risk of ISR recurrence.

Study limitations. Although enrolling all consecutive patients treated with SES was strongly encouraged in all participating centers, no information was collected on patients treated with SES but not enrolled in the e-SELECT registry. Also, the use of other stents than SES during the index procedure was an exclusion criterion. Both these factors may have contributed to some degree of selection bias. Some relevant variables, such as elapsed time to ISR and final dilation pressure, were not captured in the database, and, therefore, their potential influence on outcome could not be determined. Potential differences according to the underlying DES could not be established due to small patient cohorts. We monitored the source data collected in a random sample representing 20% of the patients enrolled in e-SELECT registry. Although this compares favorably with other recent stent registries, the underreporting of adverse events remains a potential limitation. The follow-up period was only 1 year. Thus, it is possible that the relative risks of ST are different over a longer period, especially because compliance with dual antiplatelet therapy would be expected to drop significantly beyond the 1-year time point. The lack of an independent core lab to assess angiographic results might lead to inappropriate assessment of restenosis type, residual stenosis, and other import angiographic variables here reported based on visual assessment from the local sites. Late angiography evaluation was not systematically obtained and only the visual angiographic analysis obtained at the sites was available. Finally, we did not compare the use of SES to

other contemporary strategies, such as the use of different DES or drug-coated balloons.

Conclusions

In the challenging scenario of percutaneous treatment of ISR, use of SES was shown to be feasible, safe, and associated with an acceptably low recurrence of adverse events (1-year combined MACE rate <10% for both cohorts). However, ISR recurrence in patients with DES ISR was relatively high (6.9%) and over twice as frequent as with BMS ISR, suggesting that other treatment strategies may be needed.

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Key Words: in-stent restenosis ■ sirolimus-eluting stent(s) ■ target lesion revascularization.

APPENDIX

For a list of collaborators, please see the online version of this article.