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Long-term outcomes following drug-eluting balloons versus thin-strut drug-eluting stents for treatment of recurrent restenosis in drug-eluting stents

Short title: DEB and thin-DES in recurrent in-stent restenosis

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WHAT'S NEW?

Despite multiple advances in coronary stent design and implantation techniques, in-stent restenosis remains a significant clinical issue. Recurrence of in-stent restenosis is a rare event, but still little is known on its optimal treatment. Our multicenter retrospective analysis of two most widely applied strategies suggests that implantation of another drug-eluting stent in the restenotic lesion might be preferred over the use of a drug-eluting balloon, as it helps avoid future revascularizations.

ABSTRACT

Background: There is limited data on the optimal revascularization strategy in patients with recurrent in-stent restenosis (R-ISR).

Aims: To compare the long-term outcomes of patients treated with either a thin-strut DES (thin-DES) or a drug-eluting balloon (DEB) for R-ISR in a drug-eluting stent (DES).

Methods: A multicenter DEB-DRAGON registry was used to retrospectively identify patients with R-ISR who received either a thin-DES or a DEB. Propensity score matching was applied to adjust for baseline differences. Primary outcome was target lesion revascularization (TLR).

Results: Out of 311 patients (mean age 67 years, 63% male) with R-ISR, 86 (27.7%) were treated with a thin-DES and 225 (72.3%) with a DEB. Median follow-up was 2.6 years. TLR occurred in 18 (20.9%) of patients who received thin-DES and 61 (27.1%) patients treated with DEB (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.33–0.98; log-rank P = 0.04). The difference remained significant in a propensity score-matched cohort of 57 patients treated with thin-DES and 57 patients treated with a DEB (17.5 vs. 33.3% respectively; HR, 0.38; 95% CI, 0.17–0.86; P = 0.01). The risks of device oriented adverse cardiac events and all-cause mortality were similar after thin-DES or DEB in both unadjusted and propensity score-matched

cohorts. In a multivariable Cox proportional hazard model the treatment with a thin-DES was an independent predictor of a TLR-free survival (HR, 0.33; 95% CI 0.13–0.84; *P* = 0.02).
Conclusions: In patients with R-ISR implantation of a thin-DES is associated with lower risk of repeated revascularization compared with angioplasty with a DEB.

Key words: recurrent in-stent restenosis, drug-eluting stent, drug-eluting balloon, percutaneous coronary intervention, revascularization

INTRODUCTION

Recurrent in-stent restenosis (R-ISR) is defined as a second event of ISR after successful treatment of an initial ISR lesion [1]. Despite advances in stent technology and implantation technique still up to 12% of patients undergoing percutaneous coronary intervention (PCI) with current drug eluting stents (DES) experience target lesion failure within 5 years, with majority of those events attributed to ISR [2]. There is very limited data on the prevalence of R-ISR, which was observed in at least 1.4% of all patients undergoing PCI in a large retrospective cohort [3]. While implantation of another stent or use of a drug-eluting balloon (DEB) are both valid strategies with similar effectiveness in the first occurrence of ISR, the preferred approach to R-ISR is debatable [4]. Specific concerns of stenting include adding another layer of metallic scaffolding, which may lead to progression of luminal narrowing and increased risk of thrombotic events. Conversely, use of DEB may be associated with mechanical complications, has limited potential of reducing the neointimal tissue burden and has recently been associated with excess mortality in the context of peripheral interventions [5, 6]. Moreover, according to current guidelines, R-ISR should prompt consideration of surgical revascularization [7]. Hence, the results of trials evaluating treatment of first ISR could not be directly extrapolated to R-ISR. Additionally, data on the management of R-ISR come mostly from the BMS and first-generation DES era with limited experience with new-generation thin-strut DES (thin-DES) [8]. Therefore we aimed to utilize the data from the contemporary DEB-DRAGON registry (NCT04415216) in order to compare the outcomes of DEB and thin-strut DES in treatment of R-ISR.

METHODS

Population

The DEB-DRAGON is a multicenter observational registry conducted in thirteen high-volume catheterization laboratories in Poland, which collected data of patients with coronary ISR

treated with PCI between February 2008 and October 2019. Long-term follow-up was obtained from the National Health Fund. Current analysis utilized the DEB DRAGON registry to select patients with R-ISR in previously implanted DES (i.e. with one or more stent layers present within the lesion). Patients with first incidence of ISR, ISR in a bare-metal stent or in bypass grafts, treated with a thick-strut DES, patients who were treated with both stent and a drug-eluting balloon, as well as those who underwent simultaneous PCI of multiple coronary territories were excluded. Derivation of the final study cohort is shown in Figure 1. Patients were divided into two groups according to the type of interventional treatment received at the time of R-ISR: a thin-DES (strut thickness <100 μm) or a paclitaxel-eluting DEB. The following thin-strut stents were used: Xience (Abbott Vascular Devices, Santa Clara, CA, US), Resolute (Medtronic CardioVascular, Santa Rosa, CA), Promus (Boston Scientific, Natick, MA, US), Synergy (Boston Scientific, Natick, MA, US), Orsiro (Biotronik AG, Bulach, Switzerland), Alex (Balton, Warszawa, Poland). The paclitaxel-DEB types were: Agent (Boston Scientific, Natick, MA, US), Elutax(Aachen Resonance GmbH, Aachen, Germany), Essential (iVas-cular, Barcelona, Spain), In.Pact (Medtronic Vascular, Santa Clara, CA, US), Pantera Lux (Biotronik AG, Buulach, Switzerland), Restore DEB (Cardionovum GmbH, Bonn, Germany), SeQuent Please Neo (B.Braun Interventional Group, Ltd, Melsulgen, Germany). All PCIs were performed by certified interventional cardiologists in accordance with standard procedures at each catheterization laboratory. No routine angiographic follow-up was recommended. The patients' data were anonymized in each center, combined into a database, and statistically analyzed as a single cohort. Chronic kidney disease was defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2, hyperlipidemia as low-density lipoprotein cholesterol concentration >116 mg/dl or current lipid-lowering treatment, hypertension as blood pressure >140/90 mm Hg or current antihypertensive treatment, peripheral artery disease as prior lower limb or carotid revascularization or current ischemic symptoms with >50% vessel luminal stenosis. The study was approved by the local ethics committees of each participating center. The patient's data was protected according to the requirements of Polish law, GDPR, and hospital Standard Operating Procedures. The study was conducted in accordance with the Declaration of Helsinki.

Endpoints

The primary endpoint was target lesion revascularization (TLR). Secondary endpoints were target vessel revascularization (TVR), myocardial infarction (MI), all-cause death and device-

oriented adverse cardiac events (DOCE, including: cardiac death, TLR, and target vessel MI). All endpoints were defined according to the definitions of endpoints for clinical trials [9]

Statistical analysis

Continuous variables were presented as means with standard deviations and compared with Student's t-test in case of normal distribution. Variables with non-normal distribution were presented as medians and interquartile ranges and compared with Mann-Whitney-U test. Normality was assessed with Kolmogorov-Smirnov test. Discrete variables were expressed as counts and percentages and compared with χ^2 test. Crude incidence of adverse events was presented with Kaplan-Meier survival curves and compared with a long-rank test. Propensity-score matching with nearest neighbour method was used to adjust for baseline differences. The variables selected for matching are listed in the Supplementary material, *File S1*. The validity of logistic regression was assessed using the Hosmer-Lemeshow goodness-of-fit test. The model was well calibrated ($\chi^2 = 4.13$; $P = 0.85$). The propensity model yielded a concordance index (C-index) of 0.75 (95% confidence interval [CI], 0.70–0.81). The association of treatment and selected variables with TLR were assessed with Cox proportional hazard model using backward multivariable procedure in the matched population. Hazard ratios (HR) with the corresponding 95% CI were estimated. A test for non-proportionality of hazards based on Schoenfeld residuals did not reveal violations of the proportionality assumptions. Two-sided *P*-value <0.05 was considered significant. The statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, US).

RESULTS

The final analysis included 311 patients with DES-ISR, of whom 86 (mean age [standard deviation, SD], 65.3 [10.0] years, 69.7% male) received a thin-DES and 225 (mean age [SD], 67.7 [9.9] years, 67.1% male) were treated with a DEB. There were substantial differences in terms of baseline clinical characteristics (Table 1). The prevalence of insulin-dependent diabetes mellitus (4.6 vs. 19.1%; P <0.01) and chronic kidney disease (17.1 vs. 31.1%; P = 0.02) was lower in patients treated with thin-DES compared with DEB, while hypertension (96.5 vs. 89.3%; P = 0.04) and current smoking (30.2 vs. 19.1%; P = 0.04) were more frequent in thin-DES compared with DEB group. Around two-thirds of patients were treated for a second and one-third for the third or further episode of ISR within the same lesion. The angiographic characteristics were similar, with the exception of more frequent final post-PCI TIMI-3 flow (100 vs. 93.8%; P = 0.01) and fewer patients with only one layer of previously implanted stents

(20.9 vs. 44.9%; *P* <0.001) in patients treated with thin-DES compared with DEB (Table 2). Dual antiplatelet treatment was prescribed for longer period in patients treated with thin-DES. The median follow-up was 31 months (range 2–121 months). The primary endpoint of TLR occurred in 18 (20.9%) of patients who received thin-DES and 61 (27.1%) patients treated with DEB (hazard ratio [HR], 0.57; 95% CI 0.33–0.98; log-rank *P* = 0.04) (Figure 2). There was no significant difference between the thin-DES and DEB group in terms of secondary endpoints including DOCE (27.9 vs. 31.1%; *P* = 0.12), TVR (27.9 vs. 31.1%; *P* = 0.11), MI (20.9 vs. 20.9%; *P* = 0.29), and all-cause death (11.6 vs. 4.9%; *P* = 0.25 respectively) (Figure 3A–D). The rates of each component of DOCE were similar among both groups (Table 3).

Propensity score matching yielded 57 well-matched pairs of patients who received a thin-DES or DEB. Baseline clinical and angiographic differences were balanced with no significant between-group difference (Tables 1 and 2). The primary endpoint of TLR was less prevalent in patients who received thin-DES compared with those treated with DEB (17.5 vs 33.3% respectively; HR, 0.38; 95% CI, 0.17–0.86; *P* = 0.01). Similarly, the risk of TVR was lower in patients treated with a thin-DES compared with a DEB (24.6 vs. 40.3% respectively; HR, 0.47; 95% CI, 0.24–0.94; *P* = 0.03). The difference favouring thin-DES over DEB in terms of DOCE did not meet statistical significance (22.8 vs. 33.3% respectively; HR, 0.52; 95% CI, 0.25–1.09; *P* = 0.07) and was mainly driven by repeated revascularizations. There was no difference in terms of MI, all-cause- and cardiac mortality between patients who received thin-DES compared with DEB (Table 3, Central illustration). Multivariable Cox proportional hazard analysis with backward selection of variables performed on the matched sample demonstrated that treatment with thin-DES was an independent predictor of freedom from TLR (HR, 0.33; 95% CI, 0.133–0.841; *P* = 0.02), along with shorter length of original stent, hypertension, R-ISR in the non-LMCA location and presentation with NSTEMI (Table 4).

DISCUSSION

To our best knowledge this is largest study to date examining the long-term outcomes after treatment of recurrent ISR with a thin-strut DES or a DEB. The main findings of our analysis are as follows: (1) R-ISR in DES is associated with high risk of future cardiac events, especially of repeated revascularizations; (2) interventional treatment of recurrent R-ISR in DES with a thin-strut DES results in fewer subsequent target lesion revascularizations compared with treatment with a DEB, and (3) both treatment modalities were associated with similar long-term risk of device-oriented composite endpoint as well as of all-cause and cardiovascular mortality.

The data on long-term outcomes after PCI for R-ISR are not well known. In a study by Kubo et al. the 4-year incidence of TLR after implantation of DES for R-ISR was 27.6%, in line with the frequency of 20.9% at almost 3 years observed in our study [10]. However, in an analysis by Kawamoto et al. [11] the frequency of TLR at 2 years was 27.7% for DES and 38.3% for DEB. Theodoropoulos et al. reported even higher incidence of TLR of 45% at 2- years after treatment of recurrent ISR [3]. These excessive event rates can be attributed to including only patients with ISR with two preexistent metallic stent layers, which was not a prerequisite in our study. However, the incidence of TLR observed in our study (20.9% and 27.1% for thin-DES and DEB) is still higher than reported after treatment of *de novo* coronary lesions even with new-generation DES (from 5.0% to 11.9% of TLR at 5 years) prompting close post-procedural follow-up [2, 12]

The results of our analysis suggest superiority of thin-DES over DEB in the treatment of R-ISR in terms of the need for future target lesion revascularizations. This finding substantially differs from the results of our prior study of patients with a first episode of ISR, in which there was no advantage of either thin-DES and DEB in the propensity-score matched groups regarding any of the long-term outcomes [13]. In the absence of randomized trials evaluating patients with recurrent ISR, all available evidence comes from retrospective analyses, which so far yielded largely conflicting conclusions. Similarly to our findings, a signal towards superiority of DES compared with DEB was observed in the previously mentioned study by Kawamoto et al. [11](27.7 vs. 38.3% of TLR at 2 years respectively), which did not meet statistical significance, possibly due to smaller sample size. On the other hand, in a report by Wang et al. [14] (n = 172) the 1-year incidence of TLR was significantly higher after DES compared with DEB (27.8 vs. 15.1%; $P = 0.04$ respectively). Interestingly, there were no baseline differences between study groups and thus no statistical adjustment was done. Compared with both these studies our analysis has larger sample size due to multicenter design and longer follow-up.

Treatment of recurrent ISR with stent implantation remains controversial, since adding yet another metallic layer inside the vessel may lead to potential decrease of lumen area and progressive luminal obstruction. However, this is the case mostly in heavily resistant calcified lesions interfering with proper stent expansion [15]. In more compliant lesions new-generation thin-strut DES may provide a benefit of larger lumen area while maintaining the radial force. We therefore hypothesize that restricting our analysis only to new generation thin-strut DES, might be a factor contributing to improved long-term-outcomes in comparison with DEB.

Recent metaanalyses raised some important concerns about excess late mortality associated with the use of paclitaxel-eluting balloons for peripheral interventions [6, 16]. The potential

explanation of the dose-dependent association between the drug and mortality was systemic toxicity of high-dose crystalline paclitaxel delivered with larger peripheral angioplasty balloons. This finding was not confirmed for similar devices used for coronary revascularization, which contain significantly less drug [17]. Similarly, our analysis did not show any excess mortality associated with DEB. On the contrary, there was numerically fewer deaths in patients treated with DEB compared with thin-DES (4.9 vs. 11.6%) which was not statistically significant.

LIMITATIONS

Obtaining adequate sample size required including patients treated with different types of DES as well as several DEB platforms. Moreover, despite current recommendations, the use of intravascular imaging in our cohort was infrequent which precluded precise characterization of underlying ISR mechanism and subsequent tailored therapy [18]. Other available technologies postulated for the management of recurrent ISR such as intravascular brachytherapy, laser atherectomy, ultra-high pressure balloon dilatations and intravascular lithotripsy were not evaluated. Furthermore, details on the use of cardiovascular medications as well as on the control of hypertension and the prevalence of periprocedural myocardial infarction are not available in the DEB-DRAGON registry. Due to retrospective study design even propensity score matching cannot fully exclude the influence of unmeasured confounders on the study results. Finally, operator's experience may influence the outcomes in this unique group of patients, especially in light of high anatomical disease complexity [19]. However, data on the operator's volume was not available in the registry.

CONCLUSIONS

In patients with recurrent DES ISR treatment with implantation of a thin-strut DES was superior to the use of DEB in terms of long-term risk of target lesion revascularization with similar risk of myocardial infarction as well as all-cause and cardiovascular mortality.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

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Table 1. Patients characteristics and clinical presentation according to the type of device

	Unmatched population			**Propensity score-matched population**		
	DEB n = 225 (72.3%)	**Thin-DES n = 86 (27.7%)**	***P*-value**	**DEB n = 57**	**Thin-DES n = 57**	***P*-value**
Demographic data						
Age, years, mean (SD)	67.7 (9.9)	65.3 (10.0)	0.06	66.2 (9.7)	65.9 (11.4)	0.87
Male gender	151 (67.1)	57 (66.3)	0.89	39 (68.4)	37 (48.7)	0.69
BMI, kg/m^2, mean (SD)	28.5 (4.6)	27.6 (3.8)	0.22	27.2 (3.9)	27.4 (3.8)	0.82
Discharge diagnosis						
Chronic coronary syndrome	74 (32.9)	20 (23.3)	0.27	18 (31.6)	15 (26.3)	0.54
Unstable angina	97 (43.1)	39 (45.3)		28 (49.1)	23 (40.3)	
NSTEMI	49 (21.8)	23 (26.7)		10 (17.6)	16 (28.1)	
STEMI	5 (2.2)	4 (4.6)		1 (1.7)	3 (5.3)	
CAD history						

Previous MI	169 (75.1)	64 (74.4)	0.90	37 (64.9)	41 (71.9)	0.42
Previous CABG	67 (29.8)	21 (24.4)	0.35	17 (29.8)	14 (24.6)	0.53
Risk factors and comorbidities						
Diabetes mellitus — Requiring insulin	110 (48.9) 43 (19.1)	34 (39.5) 4 (4.6)	0.14 <0.01	18 (31.6) 5 (8.8)	23 (40.3) 4 (7.0)	0.33 1.00
Hypertension	201 (89.3)	83 (96.5)	0.04	55 (96.5)	55 (96.5)	1.00
Hyperlipidemia	184 (81.8)	71 (82.6)	0.87	47 (82.5)	47 (82.5)	1.00
Chronic kidney disease — On dialysis	70 (31.1) 3 (1.3)	15 (17.1) 0 (0.0)	0.02 0.56	9 (15.8) 0 (0)	12 (21.1) 0 (0)	0.47 NA
Atrial fibrillation	42 (18.7)	9 (10.5)	0.08	6 (10.5)	8 (14.0)	0.57
Current smoker	43 (19.1)	26 (30.2)	0.04	15 (26.3)	14 (24.6)	0.83
Family history of CAD	50 (24.9)	25 (29.1)	0.46	16 (32.0)	17 (29.8)	0.81
Pulmonary disease	21 (9.3)	12 (13.9)	0.24	7 (12.3)	7 (12.3)	1.00
Peripheral artery disease	48 (21.3)	14 (16.3)	0.32	13 (22.8)	8 (14.0)	0.23
Left ventricular ejection fraction, %, mean (SD)	48.9 (11.4)	46.8 (10.8)	0.14	48.4 (11.0)	48.0 (9.8)	0.84
Time to ISR, months, median (IQR)	18.0 (7.0–36.0)	18.6 (10.3–40.8)	0.19	18.3 (7.0–41.0)	18.6 (10.8–32.5)	0.60
Current ISR event						
Second	145 (64.4)	54 (62.8)	0.79	34 (60.7)	38 (66.7)	0.51
Third or further	80 (35.6)	32 (37.2)		22 (39.3)	19 (33.3)	
Type of stent with ISR	N = 90	N = 20		N = 27	N = 14	

First-generation DES						
SES	4 (57.1)	2 (33.3)	0.592	1 (50.0)	3 (75.0)	1.0
PES	3 (42.9)	4 (66.7)		1 (50.0)	1 (25.0)	
Second-generation DES						
SES	13 (15.7)	5 (38.5)	0.007	4 (16.0)	5 (50.0)	0.13
BES	1 (1.2)	2 (15.4)		1 (4.0)	1 (10.0)	
ZES	16 (19.3)	0		2 (8.0)	0 (0)	
EES	53 (63.9)	6 (46.2)		18 (72.0)	4 (40.0)	

Values are mean (SD), median (IQR) or n (%)

Abbreviations: BES, biolimus-eluting stent; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; DEB, drug eluting balloon; DES, drug eluting stent; EES, everolimus-eluting stent; ISR, in stent restenosis; MI, myocardial infarction; NA, not available; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; kidney disease = eGFR <60 ml/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease (MDRD) method; hyperlipidemia was defined as low-density lipoprotein cholesterol concentration >116 mg/dl or current lipid-lowering treatment, hypertension was defined as blood pressure >140/90 mm Hg or current antihypertensive treatment, peripheral artery disease was defined as as prior lower limb or carotid revascularization or current ischemic symptoms with >50% vessel luminal stenosis; SES, sirolimus-eluting stent; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting-stent; ZES, zotarolimus-eluting stent

Table 2. Angiographic and procedural data according to the type of device

	Unmatched population			**Propensity score-matched population**		
	DEB n = 225 (72.3%)	**Thin-DES n = 86 (27.7%)**	***P*-value**	**DEB n = 57**	**Thin-DES n = 57**	***P*-value**

Angiography						
1-vessel disease	135 (60.0)	46 (53.5)	0.24	33 (57.9)	33 (57.9)	0.82
2-vessel disease	57 (25.3)	30 (34.9)		16 (28.1)	18 (31.6)	
3-vessel disease	33 (14.7)	10 (11.6)		8 (14.0)	6 (10.5)	
Bifurcation	30 (13.3)	8 (9.3)	0.33	9 (15.8)	7 (12.3)	0.59
Thrombus	2 (0.9)	3 (3.5)	0.13	1 (1.7)	0 (0.0)	1.00
Severe calcification	4 (1.8)	3 (3.5)	0.40	2 (3.5)	3 (5.3)	1.00
Diameter stenosis, %, mean (SD)	84.0 (11.7)	84.0 (8.8)	0.97	80.9 (12.5)	83.5 (8.6)	0.20
Target lesion						
Left main	13 (5.8)	6 (7.0)	0.69	7 (12.3)	5 (8.8)	0.54
Left anterior descending	104 (46.2)	39 (45.3)	0.89	24 (42.1)	25 (43.9)	0.85
Left circumflex	102 (45.3)	39 (45.3)	0.99	27 (47.4)	29 (50.9)	0.71
Right coronary artery	117 (52.0)	54 (62.8)	0.09	28 (49.1)	29 (50.9)	0.85
Original stent-length, mm; mean (SD)	24.3 (9.6)	21.3 (7.8)	0.10	26.1 (10.9)	20.9 (8.0)	0.06
Original stent-diameter, mm; mean (SD)	3.1 (0.5)	3.0 (0.4)	0.81	2.9 (0.5)	3.0 (0.4)	0.32
Prior stent layers						
1	101 (44.9)	18 (20.9)	<0.001	22 (38.6)	13 (22.8)	0.16
2	94 (41.8)	51 (59.3)		24 (42.1)	33 (57.9)	
>2	30 (13.3)	17 (19.8)		11 (19.3)	11 (19.3)	
ISR morphology						
Focal	107 (50.0)	42 (48.8)	0.16	26 (46.4)	29 (50.9)	0.53

Diffuse	79 (36.9)	28 (32.6)		23 (41.1)	18 (31.6)	
Proliferative	20 (9.4)	15 (17.4)		5 (8.9)	9 (15.8)	
Occlusive	8 (3.7)	1 (1.2)		2 (3.6)	1 (1.7)	
Balloon pre-dilatation						
Length, mm, mean (SD)	16.5 (4.0)	16.2 (4.7)	0.64	15.9 (3.2)	15.9 (5.0)	0.98
Diameter, mm, mean (SD)	3.0 (0.6)	2.9 (0.7)	0.62	2.9 (0.5)	2.9 (0.8)	0.88
Device data						
Length, mm, mean (SD)	22.2 (6.6)	20.7 (9.1)	0.17	21.5 (7.0)	21.1 (8.9)	0.80
Diameter, mm, mean (SD)	3.1 (0.5)	3.1 (0.5)	0.70	3.0 (0.4)	3.1 (0.5)	0.22
Post-procedure						
Residual stenosis	21 (9.3)	9 (10.5)	0.76	9 (15.8)	5 (8.8)	0.25
TIMI 3	211 (93.8)	86 (100)	0.01	57 (100)	57 (100)	NA
Complications						
Perforation	1 (0.4)	0 (0.0)	1.00	0 (0)	0 (0)	NA
Dissection	6 (2.7)	2 (2.3)	1.00	0 (0)	2 (3.5)	0.49
No-reflow	2 (0.9)	0 (0.0)	1.00	0 (0)	0 (0)	NA
Intracoronary imaging	12 (5.3)	6 (7.0)	0.59	1 (1.7)	5 (8.8)	0.21
Duration of DAPT after PCI						
<3 months	37 (16.4)	3 (3.5)		5 (8.8)	3 (5.3)	
4–6 months	31 (13.8)	12 (13.9)	<0.01	6 (10.5)	9 (15.6)	0.58
7–12 months	157 (69.8)	71 (82.6)		46 (80.7)	45 (78.9)	
Pharmacotherapy at discharge						
Clopidogrel	194 (86.2)	73 (84.9)	0.76	46 (80.7)	47 (82.5)	0.81
Ticagrelor	25 (11.1)	12 (13.9)	0.49	10 (17.5)	9 (15.8)	0.80
Prasugrel	3 (1.3)	1 (1.2)	0.91	0 (0.0)	1 (1.7)	1.00

Oral anticoagulant	34 (15.1)	6 (7.0)	0.06	5 (8.8)	5 (8.8)	1.00

Abbreviations: TIMI, thrombolysis in myocardial infarction; DAPT, dual antiplatelet therapy; other — see Table 1

Table 3. Long term follow-up according to the device before and after propensity score matching

	Unmatched population						**Propensity**		
	DEB n = 225 (72.3%)	**Thin-DES n = 86 (27.6%)**	**36-month event rate (95% CI) DEB**	**36-month event rate (95% CI) DES**	**HR (95%CI) Reference: DEB**	***P*-value (log-rank)**	**DEB**	**Thin-DES**	**36-eve (95 I**
TLR	61 (27.1)	18 (20.9)	30.0 (23.9–37.1)	19.0 (9.8–28.2)	0.57 (0.33–0.98)	0.039	19 (33.3)	10 (17.5)	3 (1 4
TVR	70 (31.1)	24 (27.9)	34.4 (27.0–41.7)	24.8 (14.2–35.4)	0.69 (0.43–1.11)	0.12	23 (40.3)	14 (24.6)	4 (2 5

MI	47 (20.9)	18 (20.9)	22.0 (15.6–28.4)	18.5 (9.6–27.4)	0.78 (0.45–1.37)	0.39	13 (22.8)	11 (19.3)	(9.9
TV-MI	21 (9.3)	6 (7.0)	9.6 (5.0–14.1)	6.2 (0.9–11.6)	0.62 (0.25–1.54)	0.29	6 (10.5)	4 (7.0)	(0.4
CV Death	8 (3.6)	7 (8.1)	5.0 (1.4–8.0)	7.9 (1.8–14.0)	1.87 (0.67–5.22)	0.22	0 (0)	4 (7.0)	
All-cause death	11 (4.9)	10 (11.6)	5.1 (1.7–8.5)	10.7 (3.6–17.7)	1.67 (0.69–4.04)	0.25	2 (3.5)	5 (8.8)	(0.
DOCE	70 (31.1)	24 (27.9)	35.1 (27.7–42.6)	24.7 (14.5–34.9)	0.69 (0.43–1.10)	0.12	19 (33.3)	13 (22.8)	(4

Abbreviations: DOCE, composite of cardiac death; TLR, and target vessel MI; HR, hazard ratio; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; other — see Table 1

Table 4. Multivariable Cox proportional hazards analysis for the independent predictors of target lesion revascularization.

Variable	**HR (95% CI)**	***P*-value**
Total length of implanted stents (1 mm increment)	1.079 (1.034–1.126)	<0.001
Hypertension	0.070 (0.021–0.239)	<0.001
Lesion location in left main	8.383 (2.840–24.745)	<0.001
NSTEMI	0.166 (0.039 -0.713)	0.02
ThinDES vs. DEB	0.334 (0.133–0.841)	0.02

Harrell's concordance statistics 0.784 (95% CI, 0.683–0.885)

Abbreviations: see Table 1

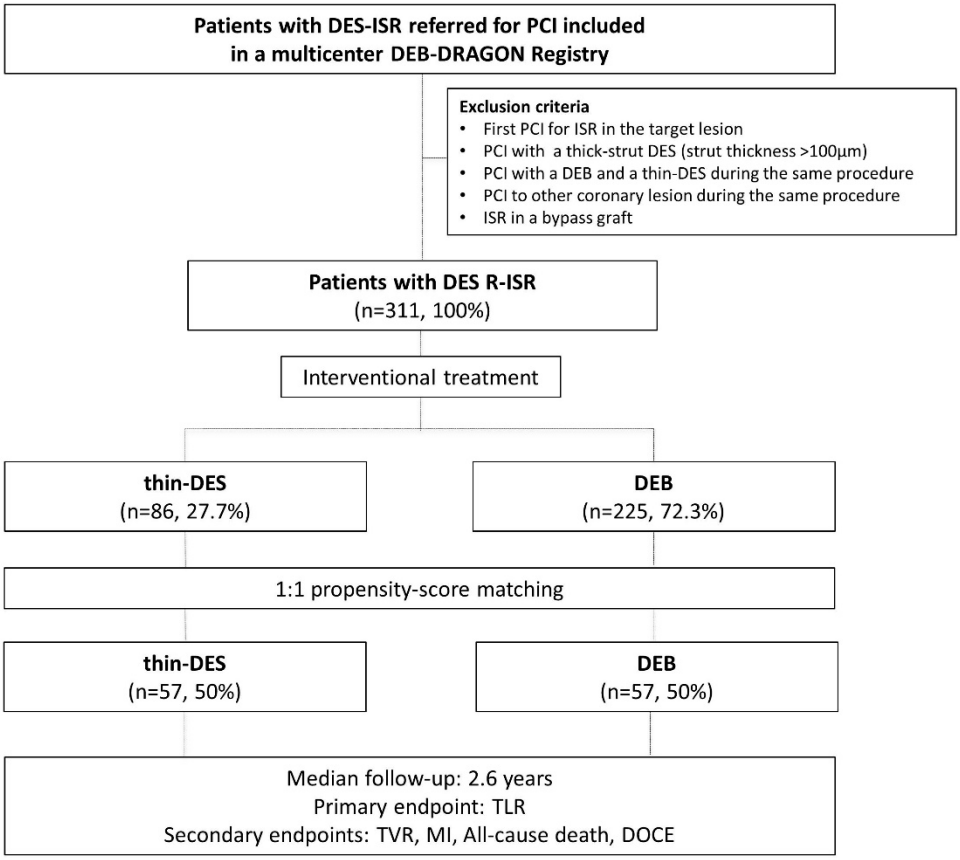


Figure 1. Study flowchart

Abbreviations: DEB, drug-eluting balloon; DES, drug-eluting stent; DOCE, device-oriented cardiac outcome (cardiac death, TLR or target vessel MI); ISR, in-stent restenosis; MI, myocardial infarction; R-ISR, recurrent in-stent restenosis; TLR, target lesion revascularization; TVR, target-vessel revascularization

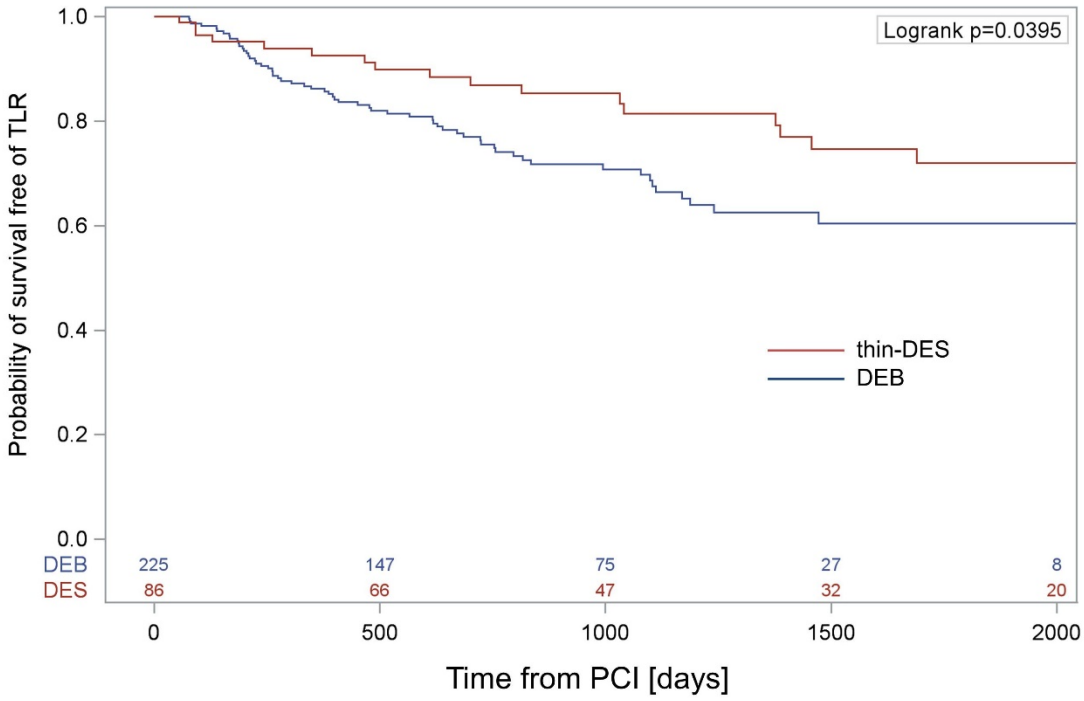


Figure 2. Kaplan-Meier survival curves for the primary endpoint of target lesion revascularization in patients treated with thin-DES and DEB

Abbreviations: PCI, percutaneous coronary intervention; other — see Figure 1

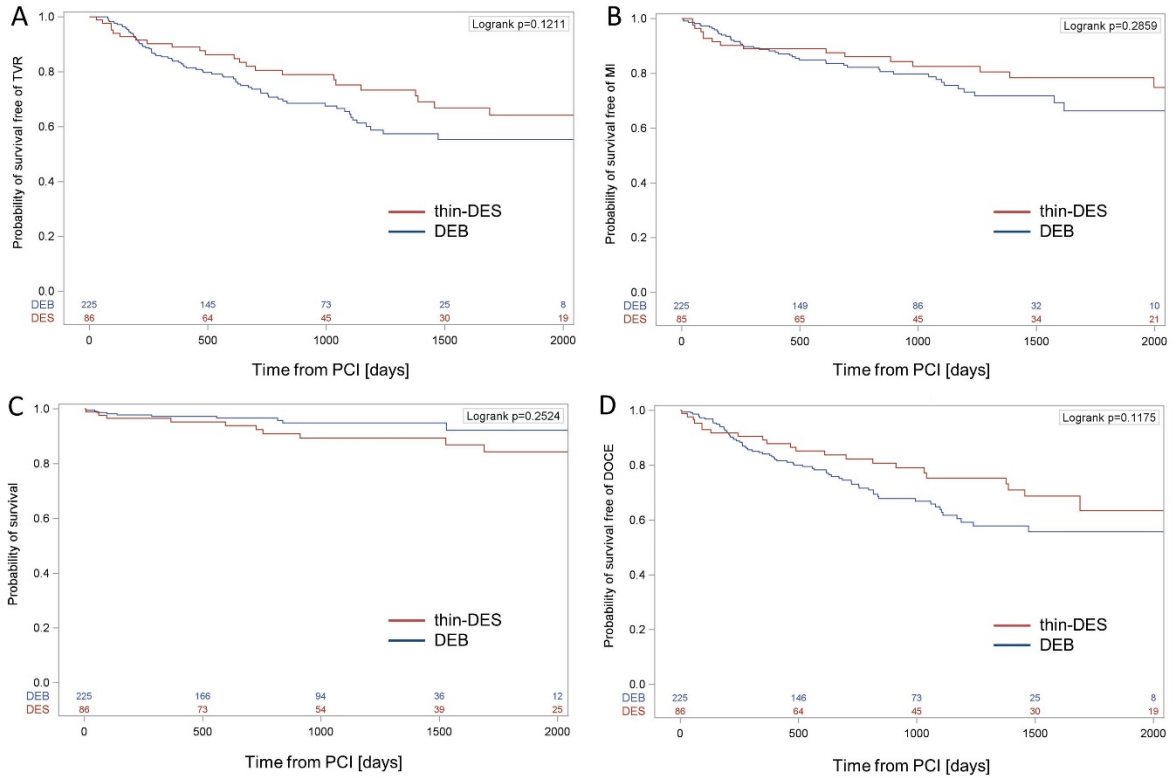
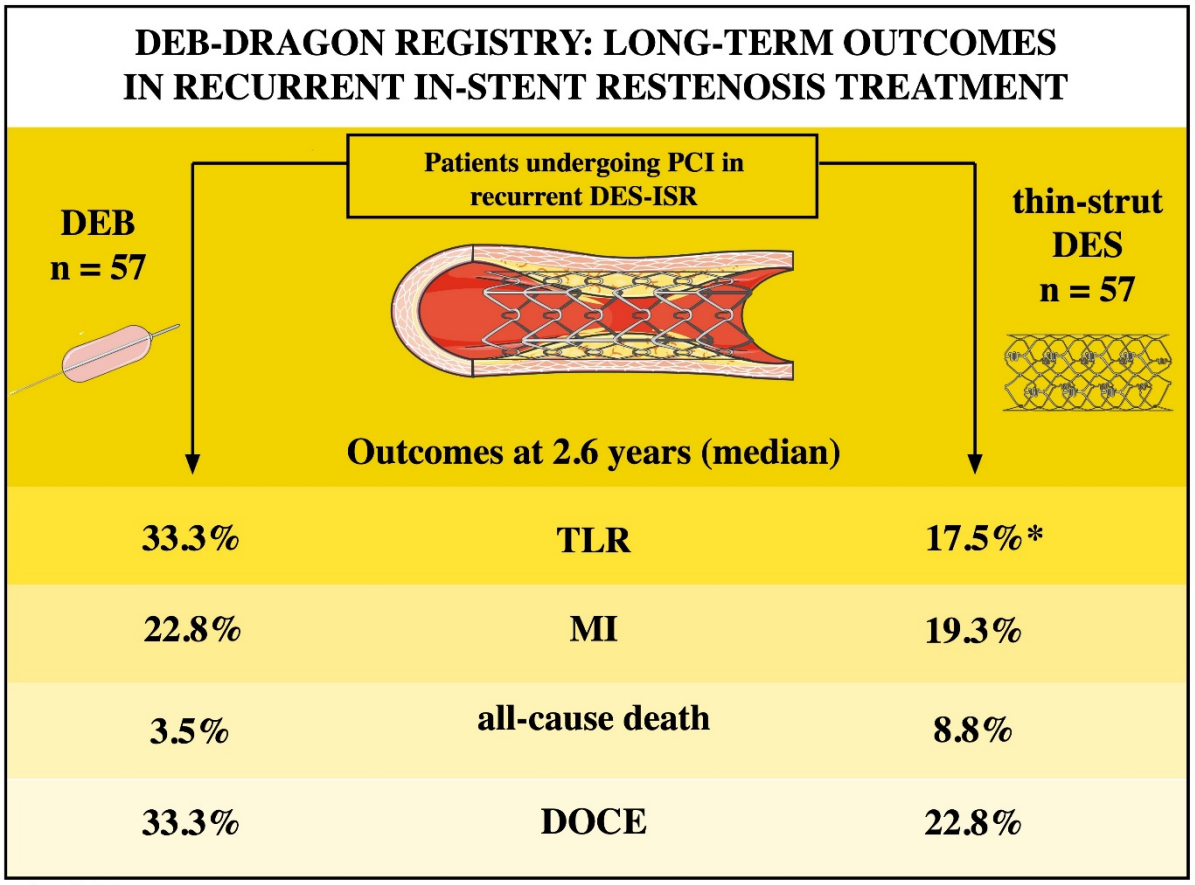


Figure 3. A. Kaplan-Meier survival curves for target vessel revascularization. **B.** Myocardial infarction. **C.** All-cause mortality and **D.** device-oriented composite outcome (cardiac death, target lesion revascularization, or target vessel myocardial infarction) in patients treated with thin-DES and DEB

Abbreviations: see Figures 1 and 2



Central illustration. Long-term outcomes following treatment of recurrent DES-ISR with either thin-DES or DEB — a propensity-score matched analysis

Abbreviations: see Figure 1