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Paclitaxel-coated balloon for the treatment of drug-eluting stent restenosis: subanalysis results from the Valentines I trial☆

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ABSTRACT

Objectives: To analyze the effect of paclitaxel-coated balloon (PCB) treatment on patients with drug-eluting stent (DES) restenosis.
Background: In the Valentines I trial, treatment of coronary in-stent restenosis was effective and safe with the second-generation DIOR® PCB.
Methods: Valentines I prospectively enrolled 250 patients with in-stent restenosis (ISR); 76 patients (30.4%) had restenosis of a previous paclitaxel or limus DES. Patients underwent balloon angioplasty followed by PCB treatment. Clinical outcomes of patients with paclitaxel-eluting DES restenosis (n = 34; 41 lesions) and limus-eluting (sirolimus, everolimus and zotarolimus) DES restenosis (n = 42; 43 lesions) treated with DIOR® PCB were compared.
Results: Baseline characteristics were similar. There were more diffuse lesions >20 mm treated in paclitaxel- compared to limus-eluting DES restenosis (50% vs. 26.8%, p = 0.032). Number of PCB used per patient (1.08 ± 0.31 overall), mean PCB diameter (2.99 ± 0.42 mm overall), mean PCB length (24.4 ± 11.9 mm overall), and bailout stenting (2.4% vs. 4.7%) were similar (p = NS). At mean follow-up of 231 ± 43 days, major adverse cardiac events was 0% vs. 23.8% in paclitaxel- vs. limus-eluting DES restenosis (p = 0.002), driven mainly by less target vessel revascularization (0% vs. 21.4%, p = 0.004). Target lesion revascularization was 0% vs. 16.7% for paclitaxel- vs. limus-eluting DES restenosis (p = 0.015).
Conclusion: In Valentines I, PCB use was more effective in patients with paclitaxel DES restenosis compared to limus DES restenosis, achieving better mid-term clinical outcomes. This suggests the efficacy of localized paclitaxel delivery to overcome paclitaxel resistance but not limus resistance due to different mechanisms of DES failure.

1. Introduction

Despite the efficacy of drug-eluting stents (DES) compared to bare metal stents (BMS) in preventing coronary restenosis, DES failure is not uncommon and presents more frequently in complex lesion subsets [1–3]. Treatment of DES restenosis remains challenging, and the optimal treatment option is unclear [4]. Several percutaneous treatment options are available. These include balloon angioplasty with regular or cutting/scoring balloons, repeat stenting with DES, vascular brachytherapy, and paclitaxel-coated balloon (PCB) angioplasty. PCB is an attractive option to treat in-stent restenosis (ISR) as it avoids another added layer of stent, and has the potential of shortened dual antiplatelet therapy (DAPT) duration without increasing the thrombosis risk [5]. PCB has been shown to be superior to plain old balloon angioplasty in both BMS and DES ISR [6–8], and non-inferior to paclitaxel-eluting DES [9,10]. However, not much is known about the differential effects of PCB on paclitaxel-eluting and limus-eluting DES restenosis. In the Valentines I trial, we demonstrated the safety and feasibility of the DIOR® (Eurocor GmbH, Bonn, Germany) PCB in treating BMS and DES restenosis [11]. We analyzed from the Valentines I cohort the clinical outcomes of using the DIOR PCB on paclitaxel-eluting DES and limus-eluting DES restenosis.

2. Methods

The Valentines I trial has been previously described and the main results published [11]. Briefly, the trial was an international,

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multicenter, prospective registry that enrolled patients over a short time frame (2/14/10–2/23/10) via an online Web-based system. Patient data from 104 centers in 26 countries were entered into an electronic data capture system, and a data monitoring structure ensured that >50% of data were verified. The study was conducted in accordance with international healthcare guidelines, as well as local laws and regulations.

2.1. Patient selection

Valentines I included 250 patients who presented with stable or unstable angina pectoris and/or documented ischemia due to an ISR (>50%) of a previously placed BMS or DES. Excluded were patients presenting with acute myocardial infarction (MI), short life expectancy (<12 months), lesions requiring additional stenting prior to PCB treatment, prior radiation therapy to target vessel, and patients unable to take dual antiplatelet therapy (DAPT) for ≥3 months. In this analysis, we included 76 patients from the Valentines I cohort who presented with DES restenosis (identified as either paclitaxel DES or limus DES restenosis), were treated with the DIOR PCB, and had clinical follow-up data.

2.2. Interventional procedure

Enrolled patients received peri- and post-procedural aspirin (80–325 mg per day) and clopidogrel (300–600 mg loading dose, followed by 75 mg per day). Intravenous heparin was used as anticoagulation during the procedure maintained at targeted activated clotting time. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Post procedure, DAPT was recommended for ≥3 months, followed by aspirin indefinitely.

Following coronary angiography, predilatation of the ISR lesion was recommended with regular short-length balloons sized to the original stent diameter in a 0.7–0.8:1 ratio. If a good angiographic result was obtained [e.g., thrombolysis in myocardial infarction (TIMI) 3 flow and residual stenosis <30%], the DIOR balloon was inflated for ≥30 seconds at the lesion with an overlap of ≥2 mm on each edge of the predilatation balloon-treated segment. The DIOR balloon was sized to the original stent diameter in a 1:1 ratio. Special emphasis was placed on avoiding geographical miss (i.e. predilated area not covered by the PCB). Additional bailout stenting using a BMS was left to the operator's discretion in cases of suboptimal angiographic result (TIMI flow grade <3 and/or residual stenosis >30%).

The second-generation DIOR PCB used in the Valentines trial contains paclitaxel as the active drug, in a concentration of 3 μg/mm^2 of balloon surface using a shellac coating method. The un-inflated balloon is thrice-folded which protects the drug from early wash-off during balloon catheter insertion and tracking. The recommended inflation time is 30–45 seconds to achieve adequate paclitaxel delivery to the vessel wall. The DIOR balloon is available in lengths of 15–30 mm, and diameters of 2.0–4.0 mm.

2.3. Follow-up/end points

Clinical follow-up was performed 6–9 months after the index procedure. Outcomes were reported based on definitions included in the study protocol. The primary end point was the occurrence of major adverse cardiac events (MACE), defined as all-cause death, MI and target vessel revascularization (TVR). Vessel thrombosis follows the Academic Research Consortium criteria for stent thrombosis. MI was defined as any elevation of troponin (or other cardiac enzymes if troponin was not recorded) in combination with ischemic chest pain. Target lesion revascularization (TLR) was defined as any repeat revascularization (percutaneous or surgical) due to a restenosis in the PCB-treated segment (which includes 5 mm beyond the treated segments proximally and distally). TVR was defined as any repeat revascularization of the PCB-treated vessel. Device success was defined as without bailout stenting and/or without device complications; procedural success was defined as TIMI 3 flow and final residual stenosis of <30% after PCB treatment and possible bailout stenting.

2.4. Statistical analysis and manuscript preparation

Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). Continuous variables are expressed as mean ± SD. Categorical variables are expressed as frequencies and percentages. For continuous variables, the groups were compared with a parametric Student's *t* test or a nonparametric Mann–Whitney U test. Categorical variables were compared with chi-square test or Fisher's exact test as appropriate. $p < 0.05$ was considered statistically significant. Event-free survival from MACE was shown as Kaplan–Meier curves and compared using log-rank tests.

The data acquisition, data analysis and writing of the manuscript were independently generated by the principal investigators and their teams. Eurocor GmbH was involved in the clinical monitoring of recruiting sites and the review of data accuracy.

3. Results

3.1. Patient and procedural characteristics

A total of 76 patients with DES restenosis treated with DIOR PCB were analyzed. There were 34 patients (with 41 lesions) with paclitaxel-eluting DES restenosis and 42 patients (with 43 lesions) with limus-eluting DES restenosis. The limus-eluting DES restenosis group consisted of sirolimus-eluting (n = 19), zotarolimus-eluting (n = 9), and everolimus-eluting (n = 14) DES. Table 1 shows the baseline characteristics of the study population, which were similar between groups. Table 2 describes the groups' lesion characteristics. There were numerically more left anterior descending artery lesions with paclitaxel DES restenosis and more circumflex artery lesions with limus DES restenosis treated. The majority of lesions treated were in the proximal and mid segments of the target vessel. There were significantly more diffuse lesions >20 mm with paclitaxel DES restenosis compared to limus DES restenosis (50% vs. 26.8%, p = 0.032) treated with PCB. One-third of lesions treated with PCB had focal or multifocal restenosis. Proliferative and occlusive restenosis morphology constitutes a small percentage of cases treated. The majority of ISR occurred beyond 6 months of stent implantation, and the majority of lesions had one prior intervention for ISR before this current procedure. There were no differences between the 2 groups with regard to timing of restenosis and number of prior ISR interventions. Table 3 describes the procedural characteristics, which were similar between the 2 groups. Predilatation before PCB treatment was 75%. Procedural success was 100%, and device success was 96% overall. Bailout stenting occurred in 1 patient with paclitaxel DES restenosis for residual stenosis, and in 2 patients with limus DES restenosis for residual stenosis and coronary dissection.

3.2. Clinical outcomes

Table 4 shows the clinical events in the 2 groups. The mean follow-up was 231 ± 43 days. Overall MACE occurred in 10 patients (23.8%) with limus DES restenosis and in none with paclitaxel DES restenosis treated with PCB (p = 0.002). This is largely driven by differences in TVR between PCB-treated paclitaxel DES restenosis and limus DES restenosis (0 vs. 21.4%, p = 0.004). The TLR was 0 and 16.7% for PCB-treated paclitaxel DES restenosis and limus DES restenosis, respectively (p = 0.015). There was one cardiac death from the limus DES restenosis group in which the patient suffered an acute myocardial

Table 1
Patient characteristics.

Variable (patient-based)	All (n = 76)	Paclitaxel DES restenosis (n = 34)	Limus DES restenosis (n = 42)	p value
Age (years)	61.8 ± 10.3	62.6 ± 11.6	61.1 ± 9.1	0.55
Men	60 (78.9%)	29 (85.3%)	31 (73.8%)	0.22
Left ventricular ejection fraction (%)	54.3 ± 11.8	52.9 ± 9.9	55.5 ± 13.2	0.40
Risk factors				
Diabetes mellitus	29 (38.2%)	10 (29.4%)	19 (45.2%)	0.16
Insulin-treated diabetes mellitus	5 (6.6%)	2 (5.9%)	3 (7.1%)	1.00
Hypertension	61 (80.3%)	29 (85.3%)	32 (76.2%)	0.32
Hyperlipidemia	49 (64.5%)	18 (52.9%)	31 (73.8%)	0.06
Smoking (current or previous)	11 (14.5%)	7 (20.6%)	4 (9.5%)	0.20
Renal insufficiency	5 (6.6%)	4 (11.8%)	1 (2.4%)	0.17
Peripheral vascular disease	1 (1.3%)	1 (2.9%)	0	0.45
Previous myocardial infarction	23 (30.3%)	11 (32.4%)	12 (28.6%)	0.72
Previous coronary bypass surgery	11 (14.5%)	5 (14.7%)	6 (14.3%)	1.00
Clinical presentation				
Stable angina pectoris	40 (52.6%)	19 (55.9%)	21 (50.0%)	0.61
Unstable angina pectoris	18 (23.7%)	8 (23.5%)	10 (23.8%)	0.98
Positive functional stress test	19 (25.0%)	6 (17.6%)	13 (31.0%)	0.18

All values are mean ± standard deviation or n (%).

infarction 11 weeks post procedure. Late definite vessel thrombosis occurred in one patient in the limus DES restenosis group 12 weeks post procedure. Of the clinically-driven TLR, 6 patients underwent repeat PCI and 1 patient underwent coronary bypass surgery. Of the TVR-non-TLR, 2 patients underwent repeat PCI. Fig. 1 shows the Kaplan–Meier event-free survival curve for MACE. TVR rates across the different limus DES restenosis are shown in Fig. 2.

4. Discussion

The main findings of this study were: 1) differential effects on MACE, largely driven by differences in TVR, between paclitaxel DES restenosis and limus DES restenosis treated with the DIOR PCB; 2) high procedural and device success with the DIOR PCB in treating DES restenosis.

Since its introduction, the widespread use of DES in preventing coronary restenosis has led to a sizeable population of patients facing the phenomenon of DES restenosis. Moreover, DES is increasingly being implanted in complex lesions; these complex interventions predict DES restenosis [3]. The incidence of restenosis among the first-generation DES is in excess of 10% in unrestricted populations, and DES restenosis tends to occur later than BMS restenosis [1,2]. The best treatment option for DES restenosis has not yet been established. PCB as a percutaneous treatment option for DES restenosis appears promising, with results superior to balloon angioplasty and equivalent to paclitaxel DES [7–10] using the SeQuent Please (B. Braun,

Table 2
Lesion characteristics.

Variable (lesion-based)	All (n = 84)	Paclitaxel DES restenosis (n = 41)	Limus DES restenosis (n = 43)	p value
Target vessel				
Left anterior descending artery	38 (46.2%)	23 (60.0%)	15 (35.7%)	0.06
Circumflex artery	23 (27.7%)	7 (17.1%)	16 (38.1%)	0.032
Right coronary artery	22 (26.5%)	11 (26.8%)	11 (26.2%)	0.95
Target lesion location				
Ostial	2 (2.4%)	0	2 (4.7%)	0.49
Proximal	34 (40.5%)	18 (43.9%)	16 (37.2%)	0.53
Mid	34 (40.5%)	16 (39.0%)	18 (41.9%)	0.79
Distal	12 (14.3%)	6 (14.6%)	6 (14.0%)	0.93
Number of lesions per patient	1.03 ± 0.16	1.03 ± 0.17	1.02 ± 0.15	0.88
% stenosis by visual estimate	81.5 ± 15.7	82.9 ± 12.5	81.4 ± 18.0	0.76
Restenosis morphology				
Focal <10 mm, intra-stent	21 (25.9%)	8 (20.0%)	13 (31.7%)	0.23
Multifocal, intra-stent	7 (8.6%)	3 (7.5%)	4 (9.8%)	1.00
Diffuse 10–20 mm, intra-stent	17 (21.0%)	8 (20.0%)	9 (22.0%)	0.83
Diffuse >20 mm, intra-stent	31 (38.3%)	20 (50.0%)	11 (26.8%)	0.032
Proliferative, beyond stent margins	2 (2.5%)	0	2 (4.9%)	0.49
Occlusive, TIMI 0 flow	3 (3.7%)	1 (2.5%)	2 (4.9%)	1.00
Timing of restenosis				
<2 months	1 (1.2%)	1 (2.4%)	0	0.49
2–6 months	14 (16.7%)	4 (9.8%)	10 (23.3%)	0.10
6–12 months	15 (34.9%)	12 (29.3%)	15 (34.9%)	0.58
>12 months	42 (50%)	24 (58.5%)	18 (41.9%)	0.13
Number of prior ISR PCI				0.21
0	16 (19%)	10 (24.4%)	6 (14.6%)	
1	35 (41.7%)	15 (36.6%)	20 (48.8%)	
2	15 (17.9%)	10 (24.4%)	5 (12.2%)	
≥3	5 (6%)	4 (9.8%)	1 (2.4%)	
Unknown	15 (15.5%)	4 (9.8%)	9 (22.0%)	
Mean number of prior ISR PCI	1.2 ± 1.0	1.1 ± 0.7	1.3 ± 1.1	0.43

All values are mean ± standard deviation or n (%).
DES, drug-eluting stent; TIMI, thrombolysis in myocardial infarction; ISR, in-stent restenosis; PCI, percutaneous coronary intervention.

Table 3
Procedural characteristics.

Variable (lesion-based)	All (n = 84)	Paclitaxel DES restenosis (n = 41)	Limus DES restenosis (n = 43)	p value
Pre-dilatation	60 (75.0%)	26 (70.3%)	34 (79.1%)	0.37
Balloon angioplasty	55 (68.8%)	24 (64.9%)	31 (72.9%)	0.49
Cutting balloon	10 (13.5%)	3 (7.9%)	7 (19.4%)	0.19
DIOR® PCB per lesion	1.08 ± 0.31	1.09 ± 0.37	1.07 ± 0.26	0.83
Balloon diameter (mm)	2.99 ± 0.42	2.95 ± 0.37	3.02 ± 0.45	0.46
Balloon covered length (mm)	24.4 ± 11.9	26.7 ± 14.6	22.5 ± 8.8	0.14
Maximum balloon inflation pressure (atm)	12.7 ± 3.9	12.5 ± 3.9	12.8 ± 3.9	0.77
Total balloon inflation time (seconds)	72.4 ± 44.7	70.6 ± 50.7	74.0 ± 40.0	0.74
Post paclitaxel coated balloon dilatation	6 (7.5%)	4 (10.8%)	2 (4.7%)	0.41
Coronary dissection	1 (1.2%)	0	1 (2.3%)	1.00
Residual stenosis	2 (2.4%)	1 (2.4%)	1 (2.3%)	1.00
Abrupt closure	0	0	0	-
Failure (dissection and/or residual stenosis)	3 (3.7%)	1 (2.4%)	2 (4.7%)	1.00
Bailout stenting with bare metal stents	3 (3.7%)	1 (2.4%)	2 (4.7%)	1.00
% final stenosis	5.2 ± 8.2	5.1 ± 8.6	5.3 ± 7.9	0.92
Device success (DIOR strategy)	80 (96.4%)	38 (95%)	42 (97.7%)	0.61
Procedural success	84 (100%)	41 (100%)	43 (100%)	1.00

All values are mean ± standard deviation or n (%).
DES, drug-eluting stent; PCB, paclitaxel-coated balloon.

Melsungen, Germany) balloon. Several studies including the Valentines I trial have demonstrated that PCB treatment of BMS restenosis results in better treatment outcomes compared to DES restenosis [11–14]. This is perhaps due to the fact that lesions at higher risk of restenosis were initially implanted with DES rather than a BMS and perhaps because treatment failure with DES indicates a more aggressive form of "drug-resistant" proliferative process compared to the drug-naïve BMS restenosis vessel.

In our study, overall TLR (9.2%) and TVR rates (11.8%) in DIOR PCB treatment of DES restenosis were comparable to that observed in the SeQuent Please World Wide Registry (9.6% and 10.1%, respectively) [12]. However, we observed a disparity in PCB treatment outcomes, with patients presenting with limus DES restenosis doing worse than patients presenting with paclitaxel DES restenosis. Overall MACE was significantly higher in patients presenting with limus DES restenosis, mainly due to higher TLR (16.7% vs. 0, p = 0.007). Interestingly, this differential treatment effect was not observed in the SeQuent Please World Wide Registry; PCB treatment of paclitaxel DES and non-paclitaxel DES resulted in similar repeat revascularization rates (TLR, 8.3 vs. 10.8%, p = 0.46). Perhaps this underscores the need for future evaluation with regard to different mechanisms of restenosis among different stent types and their response to a further local drug elution.

In the recently published Randomized Trial of Paclitaxel-Eluting Balloon, Paclitaxel-Eluting Stent and Plain Balloon Angioplasty for Restenosis in "-Limus"-Eluting Coronary Stents (ISAR-DESIRE 3) [10], the SeQuent Please PCB was shown to be non-inferior to paclitaxel DES, and both PCB and paclitaxel DES were superior to balloon angioplasty alone in treating limus DES restenosis. The PCB arm had a TLR rate of 22.1% at 1-year follow-up. Our study compared favorably in terms of TLR (16.7%) using the DIOR PCB on limus DES restenosis. Moreover, the majority of limus DES restenotic lesions treated in our study were non-focal (59%), whereas almost 70% of lesions treated by PCB in ISAR-DESIRE 3 were focal. In our study, there were differences in the restenosis morphology. There were numerically more focal lesions treated in the limus DES restenosis, and significantly more diffuse lesions treated in the paclitaxel DES restenosis, consistent with other reported series on DES restenosis [15]. Although it has previously been reported that non-focal patterns of restenosis are associated with higher rates of TLR compared to focal (23% vs. 9.8%, p = 0.007) [16], our study suggests that the paclitaxel DES restenosis group, which contained a higher percentage of diffuse pattern of ISR treated, had less TLR than the limus DES group after PCB treatment.

Another possibility exists that more of the limus DES restenosis was due to mechanical factors such as stent fracture, and these were inadequately treated with PCB following balloon angioplasty and should in fact require another stent. Moreover, numerically more limus DES restenosis occurred less than 6 months from the last stent implantation, suggesting mechanical factors rather than drug resistance, as the underlying etiology.

A third possibility is that since sirolimus (and its analogues) is more robust in reduction of restenosis [17–19], limus-DES failure may represent a much more refractory group to treat when compared with paclitaxel failure. In this regard, perhaps drug resistance toward paclitaxel can be overcome by a further paclitaxel dosing, but drug resistance toward sirolimus and its analogues do not respond as well to a local paclitaxel dose. Theoretically a restenotic lesion should respond better with a different drug inhibiting neointimal hyperplasia via a different mechanism; however, evidence has been inconclusive for advocating such a strategy in studies evaluating the same versus different DES for treatment of DES restenosis [20–22].

The mechanisms of antiproliferation differ between paclitaxel and limus-eluting stents. Paclitaxel affects the cell cycle by binding

Table 4
Clinical events.

Variable (patient-based)	All (n = 76)	Paclitaxel DES restenosis (n = 34)	Limus DES restenosis (n = 42)	p value
Death	1 (1.3%)	0	1 (2.4%)	1.00
Myocardial infarction	1 (1.3%)	0	1 (2.4%)	1.00
Target lesion revascularization	7 (9.2%)	0	7 (16.7%)	0.015
Target vessel revascularization	9 (11.8%)	0	9 (21.4%)	0.004
Vessel thrombosis	1 (1.3%)	0	1 (2.4%)	1.00
Cumulative major adverse cardiac events*	10 (13.2%)	0	10 (23.8%)	0.002

All values are n (%).
* All-cause death, myocardial infarction and target vessel revascularization.

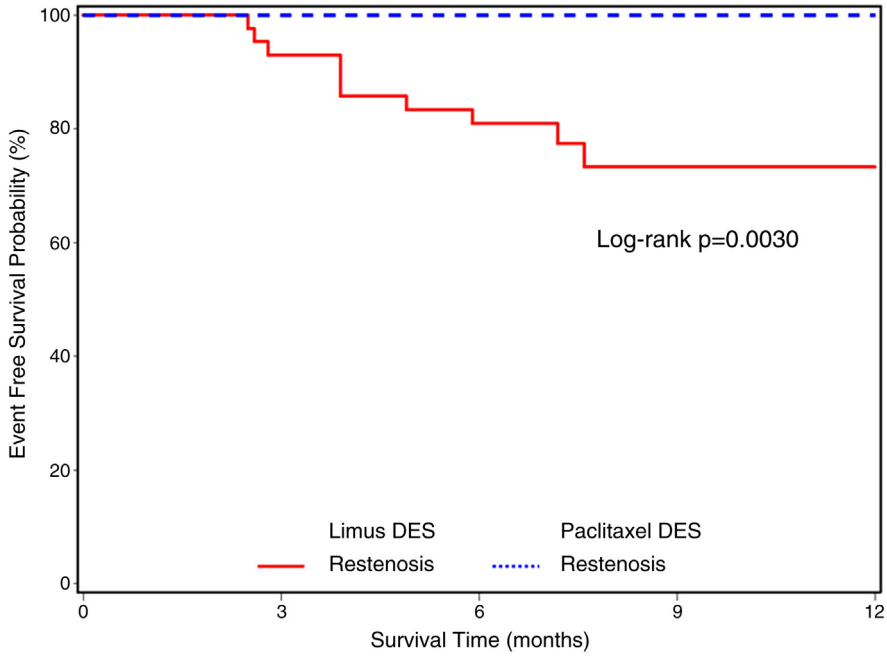

Fig. 1. Kaplan–Meier survival curve for major adverse cardiac events (MACE) comparing paclitaxel-eluting drug-eluting stent (DES) restenosis and limus-eluting DES restenosis treated with paclitaxel-coated balloon.

to the beta-tubulin subunit, which stabilizes the microtubules required for mitosis and induces a cytotoxic effect on cells. Sirolimus (and its analogues) bind to the FK-binding protein 12, which leads to inhibition of the mammalian target of rapamycin pathway that arrests the cell cycle between G1 and S1 phases causing a cytostatic effect and suppresses smooth muscle cell migration and proliferation [23]. The mechanisms of drug resistance may also differ between paclitaxel and sirolimus (and its analogues) [24,25]. More insight is required on how to overcome this pharmacologically on a cellular level.

Our study demonstrates the feasibility of using PCB as a treatment option for DES restenosis. Interventionists are familiar with the simple balloon platform, complying with the recommended inflation techniques with PCB for optimal drug delivery. Procedural success was 100% with only 3 patients requiring bailout stenting for suboptimal angiographic result. Moreover, vessel thrombosis was 1.3% on follow-up, which was similar to that reported in PEPCAD-DES [8].

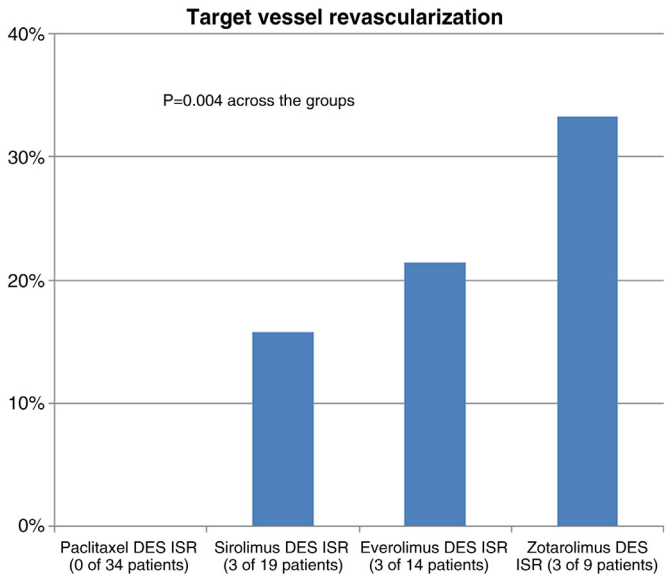

Fig. 2. Target vessel revascularization rates across different stent types. (DES, drug-eluting stent; ISR, in-stent restenosis.)

4.1. Limitations

This study was not randomized and was intended to be observational. The small patient numbers in this study also prohibit drawing definitive conclusions, especially among individual stent types. There was no quantitative coronary angiography performed at baseline for objective lesion assessment, nor was there scheduled angiography follow-up for all patients. However, it was our intention for clinically-driven revascularization, as planned angiography often leads to an inflation of revascularizations. We do not have longer-term outcomes as follow-up was limited to 9 months. Intravascular ultrasound was not part of the study protocol, so information with regard to the possible etiology of each lesion restenosis was not collected. Predilatation was not performed in all patients although it was recommended. We used the DIOR® PCB, and since we cannot assume a class effect among different PCBs, our results may not be generalized to other PCBs.

5. Conclusion

In this analysis from the Valentines I trial, the use of DIOR® PCB was more effective in patients with paclitaxel-eluting DES restenosis compared to limus-eluting DES restenosis, achieving better mid-term clinical outcomes. This suggests the efficacy of localized paclitaxel delivery to overcome paclitaxel resistance but not limus resistance due to different mechanisms of DES failure.

References

[1] Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation 2004;109:190–5.

[2] Mauri L, Silbaugh TS, Wolf RE, Zelevinsky K, Lovett A, Zhou Z, et al. Long-term clinical outcomes after drug-eluting and bare-metal stenting in Massachusetts. Circulation 2008;118:1817–27.
[3] Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113:2293–300.
[4] Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol 2010;56:1897–907.
[5] Waksman R, Pakala R. Drug-eluting balloon: the comeback kid? Circ Cardiovasc Interv 2009;2:352–8.
[6] Scheller B, Clever YP, Kelsch B, Hehrlein C, Bocksch W, Rutsch W, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. JACC Cardiovasc Interv 2012;5:323–30.
[7] Habara S, Mitsudo K, Kadota K, Goto T, Fujii S, Yamamoto H, et al. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. JACC Cardiovasc Interv 2011;4:149–54.
[8] Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. J Am Coll Cardiol 2012;59:1377–82.
[9] Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation 2009;119:2986–94.
[10] Byrne RA, Neumann FJ, Mehilli J, Pinieck S, Wolff B, Tiroch K, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet 2013;381:461–7.
[11] Stella PR, Belkacemi A, Waksman R, Stahnke S, Torguson R, von Strandmann RP, et al. The Valentines Trial: results of the first one week worldwide multicentre enrolment trial, evaluating the real world usage of the second generation DIOR paclitaxel drug-eluting balloon for in-stent restenosis treatment. EuroIntervention 2011;7:705–10.
[12] Wöhrle J, Zadura M, Möbius-Winkler S, Leschke M, Opitz C, Ahmed W, et al. SeQuentPlease World Wide Registry: clinical results of SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. J Am Coll Cardiol 2012;60:1733–8.
[13] Vaquerizo B, Serra A, Miranda-Guardiola F, Martínez V, Antoni Gómez-Hospital J, Iñiguez A, et al. One-year outcomes with angiographic follow-up of paclitaxel-eluting balloon for the treatment of in-stent restenosis: insights from Spanish multicenter registry. J Interv Cardiol 2011;24:518–28.
[14] Hehrlein C, Dietz U, Kubica J, Jørgensen E, Hoffmann E, Naber C, et al. Twelve-month results of a Paclitaxel Releasing Balloon in Patients Presenting with In-stent Restenosis First-in-Man (PEPPER) trial. Cardiovasc Revasc Med 2012;13:260–4.
[15] Corbett SJ, Cosgrave J, Melzi G, Babic R, Biondi-Zoccai GG, Godino C, et al. Patterns of restenosis after drug-eluting stent implantation: insights from a contemporary and comparative analysis of sirolimus- and paclitaxel-eluting stents. Eur Heart J 2006;27:2330–7.
[16] Cosgrave J, Melzi G, Biondi-Zoccai GG, Airoldi F, Chieffo A, Sangiorgi GM, et al. Drug-eluting stent restenosis the pattern predicts the outcome. J Am Coll Cardiol 2006;47:2399–404.
[17] Schömig A, Schömig A, Dibra A, Windecker S, Mehilli J, Suárez de Lezo J, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1373–80.
[18] Gurm HS, Boyden T, Welch KB. Comparative safety and efficacy of a sirolimus-eluting versus paclitaxel-eluting stent: a meta-analysis. Am Heart J 2008;155:630–9.
[19] Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873–91.
[20] Garg S, Smith K, Torguson R, Okabe T, Slottow TL, Steinberg DH, et al. Treatment of drug-eluting stent restenosis with the same versus different drug-eluting stent. Catheter Cardiovasc Interv 2007;70:9–14.
[21] Mehilli J, Byrne RA, Tiroch K, Pinieck S, Schulz S, Kufner S, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. J Am Coll Cardiol 2010;55:2710–6.
[22] Alfonso F, Pérez-Vizcayno MJ, Dutary J, Zueco J, Cequier A, García-Touchard A, et al. Implantation of a drug-eluting stent with a different drug (switch strategy) in patients with drug-eluting stent restenosis. Results from a prospective multicenter study (RIBS III [restenosis intra-stent: balloon angioplasty versus drug-eluting stent]). JACC Cardiovasc Interv 2012;5:728–37.
[23] Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. Circulation 2005;111:2257–73.
[24] Huang S, Bjornsti MA, Houghton PJ. Rapamycins: mechanism of action and cellular resistance. Cancer Biol Ther 2003;2:222–32.
[25] Yusuf RZ, Duan Z, Lamendola DE, Penson RT, Seiden MV. Paclitaxel resistance: molecular mechanisms and pharmacologic manipulation. Curr Cancer Drug Targets 2003;3:1–19.