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CORONARY ARTERY DISEASE

Treatment of Small Vessel Disease With the Paclitaxel Drug-Eluting Balloon: 6-Month Angiographic and 1-Year Clinical Outcomes of the Spanish Multicenter Registry

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Background*: Small vessel disease (SMD) remains a major challenge because of the increased risk of restenosis. We sought to assess the efficacy and safety of a paclitaxel-eluting balloon (PEB) in patients with SMD.*
Methods and Results*: One-hundred and four patients with native coronary lesions in small vessels treated by using a PEB were included in this prospective multicenter registry. In each case, after regular balloon dilatation, a larger PEB was inflated for a minimum of 45–60 seconds. Patients were 65 ± 10 years old, 43% diabetic, and 58% presented acutely. Angiographic success was 93% (7% bailout BMS implantation due to coronary dissection). The rate of major adverse cardiac events (MACE) at 12 months was 4.8% (1.9% cardiac death, 1.0% MI, and 2.9% TLR). One definite stent thrombosis was reported at 6 months in a patient with bailout BMS implantation. At 7 months, late loss was 0.31 ± 0.2 mm. Bail-out BMS after DEB use, was an independent predictor of MACE, HR 18.74, 95%CI (2.58–135.84) and TLR, HR 30.99, 95%CI (2.79–344.07).*
Conclusion*: The use of this PEB for the treatment of SMD provides excellent 1-year outcomes with only 4.8% MACE. The need for a bailout BMS was a strong predictor of MACE and TLR.* (J Interven Cardiol 2015;28:430–438)

Introduction

Percutaneous coronary interventions (PCI) in small vessels (≤2.8 mm) account for 35–50% of interventional procedures undertaken in patients with coronary artery disease (CAD).[1,2] In-stent restenosis remains the main limitation and is an ongoing challenge even in the DES era.[3,4] The pathophysiological explanation for this problem is that stent implantation results in arterial injury, initiating a vasculo-proliferative cascade and resulting in neointimal hyperplasia. The neointimal thickness is relatively constant and independent of stent size, as demonstrated by intravascular ultrasound. As such, absolute late luminal loss is similar across a range of vessel diameters.[5,6] As stents placed in small vessels have less room to accommodate this growth of neointimal tissue without an important reduction in luminal area, the risk of significant restenosis is high.[5,6] Although DES have considerably reduced the incidence of restenosis,[7] rates remain in double figures in this particular subgroup.[4,7,8] Critical appraisal of the published evidence highlights some safety concerns, including delayed healing and late endothelial dysfunction of the stented arterial

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segment which appear to underlie a spectrum of late adverse events following DES therapy, including stent thrombosis.[9]

In this specific scenario, paclitaxel-coated balloon (PCB) catheters may be an alternative treatment option. Although PEB therapy has shown encouraging results in certain disease subtypes,[10–16] what limited data exists to date does not demonstrate a clear role for this modality in lesions in small vessels.[17–20] The aim of this large multicenter registry was to investigate the DIOR balloon catheter (Eurocor GmbH, Bonn, Germany), a PEB without a contrast agent as a drug-carrier, in the treatment of small vessel coronary artery disease.

Methods

Patient Population. Over a period of 2 years, 104 patients with native coronary lesions in small vessels ($\leq$2.5 mm) treated using the, DIOR PEB, were included in the multicenter and prospective Spanish DIOR registry (8 Spanish centers). The registry was set-up to assess the efficacy and safety of the DIOR balloon in patients with small vessel disease ($\leq$2.5 mm). As a real world registry, only those patients presenting with cardiogenic shock or angiographic severe calcification were excluded.

Patients' informed consent was obtained for the procedure and participation in this registry.

Quantitative Coronary Angiography (QCA). QCA measurements were undertaken by a central core lab, using a validated edge detection system (Quantcor®, version 4.0, Siemens AG, Forchheim, Germany). Angiography was performed before and after all interventions in all participating centers. The Medina classification was used to describe bifurcated lesions. Angiographic success was defined as less than 50% final residual stenosis in the treated segment and the absence of more than type B coronary dissection postDIOR angioplasty. Restenosis was defined as >50% angiographic narrowing of a previously successfully treated lesion.

Procedure and Study Drug-Eluting Balloon (DIOR™). A uniform technical approach was adopted by the study centers prior to the beginning of the study. Following selective catheterization of the culprit vessel, intracoronary nitroglycerin at a dose of 200 μgr was administered. Coronary angiography was performed with at least 2 (for the right coronary artery) or 3 (for the left coronary artery) orthogonal views showing the target lesion free of foreshortening and vessel overlap.

Dilatation of the target lesion was performed in all cases before the study intervention, with the use of a nonstudy balloon. A cutting balloon was used, at the discretion of each operator. The recommended ratio balloon: artery size was 0.8:1 with a length 5 mm shorter than that of the study balloon, DIOR™. Careful inflations with increasing pressures were advised to avoid dissections. Once an optimal dilatation result was obtained (residual stenosis less than 50%, without flow-limiting dissection, less than type B coronary dissection), a 5 mm longer DIOR™ balloon was strongly recommended to avoid a "geographical miss" effect. Details of the study balloon DIOR™ have been given elsewhere.[10,21,22] In this registry, we used both generations of DIOR™ balloons which share most general properties: the drug and the dose of paclitaxel, the balloon designed with 3-folds of microporous surface ensuring good contact with paclitaxel, and a similar preparative process. However, the coating method is different. The first generation DIOR balloon had a nanoporous surface-containing microcrystals of pure paclitaxel that were then embedded on the vessel wall at the time of balloon inflation.[10,21] The second generation DIOR balloon contains shellac as a paclitaxel carrier. Shellac is an inert substance that has already been approved by the FDA as a food additive. It is mostly composed of aleuritic acid, jalaric acid, and shelloic acid. The microporous balloon surface contains a 1:1 mixture of paclitaxel and shellac. A balloon inflation time dependency study in the porcine model of coronary artery overstretch showed almost maximum tissue paclitaxel concentrations after shorter balloon inflation times of 30 seconds and release of 75% of the drug from the balloon surface, which resulted significantly higher drug concentration after 45 minutes when compared with the first generation DIOR[22] (Fig. 1). DIOR™, was used to deliver the antiproliferative drug to the vessel wall, and inflated in the same fashion as a conventional balloon. The ratio balloon:artery recommended was 1:1 and the recommended dilatation pressure was just above nominal pressure. The recommended inflation time was from 45 to 60 seconds for the second and first DIOR, respectively. So as to evaluate the absence of acute recoil, a final angiographic image was recommended 5–7 minutes after DIOR angioplasty.

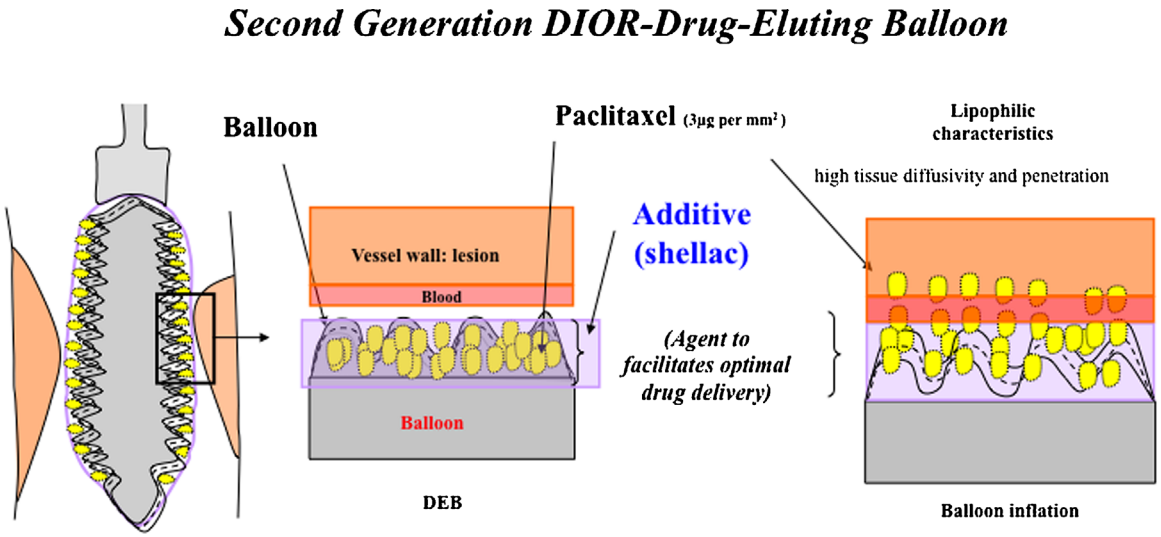

Figure 1. Second generation paclitaxel-eluting balloon design, DIOR™.

Stenting with a bare metal stent (BMS) was used only for the following indications: >type B coronary dissection, acute coronary occlusion, and acute recoil with residual stenosis more than 50%. In these cases, the type of BMS selected was left to the operator's discretion (Fig. 2).

Antithrombotic Therapy. Postprocedure patients were prescribed clopidogrel, 75 mg daily for at least 1 month and aspirin 100 mg p.o. daily indefinitely. Patients with a contraindication to dual antiplatelet therapy took either Aspirin 100 mg daily or clopidogrel 75 mg daily.

Study Definitions. Small vessel disease was defined as lesions within coronary arteries with a diameter of ≤2.5 mm by visual estimation. Myocardial infarction (MI) was defined as CPK elevation ≥3 times the upper limit of normal. Post-procedural CPK was only measured in case of symptoms and/or

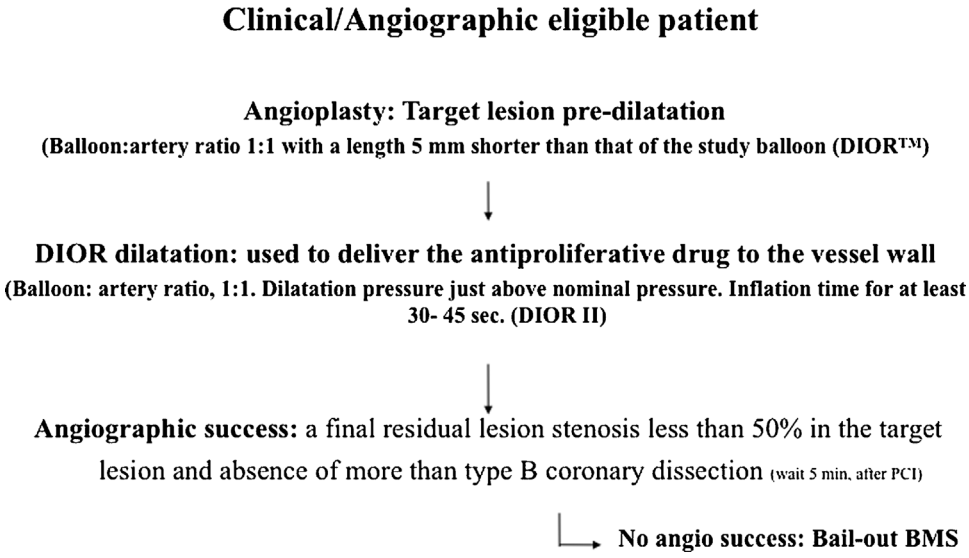

Figure 2. Study's flowchart.

electrocardiogram changes suggesting MI. Target lesion revascularization (TLR) was defined as any repeat percutaneous intervention or surgical bypass of the target lesion performed for >50% restenosis of the treated segment or within 5 mm either end of the stent. Restenosis was defined as >50% angiographic narrowing of a previously successfully treated lesion. Stent thrombosis or occlusion (ST) was defined, according to the Academic Research Consortium (ARC), as definite, probable, or possible and as early (0–30 days), late (31–360 days), or very late (>1 year) of the index PCI.[23] Deaths from undetermined causes were classified as cardiac. Major adverse cardiac events (MACE) was a combined endpoint of cardiac death, Q, or nonQ wave myocardial infarction (MI) or TLR according to the device oriented MACE definition.[23]

Follow-Up Procedures of Patients. All patients were followed by clinical visit or telephone call at 1 month, 6 months, and 1 year. At 6–8 months, in 2 preselected centers (H. Mar and H. Trias I Pujol), angiographic follow-up was performed. By predefining these 2 centers the aim was to complete a high proportion of angiographic follow-up (>80%) so as to be representative of symptomatic and asymptomatic restensosis. If a patient was lost to follow-up, the family physician or cardiologists were contacted. In case of failure, information about death was obtained from the population registry (Fig. 3).

Statistical Analysis. Continuous variables are presented as mean and standard deviation and categorical variables as number and percentage. Comparisons of continuous variables between groups were made using Student's t-test. Categorical variables were compared using either the chi-squared or Fishers exact test. For each of the events of interest considered, observation time started at the date of stent implantation and ended either at the date of occurrence of the event or on the last day of contact depending on which occurred first. Survival curves were estimated by the Kaplan–Meier method. Cox proportional hazards models were fitted for selected comparisons of outcomes by patient, lesion or procedural characteristics. A P-value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using commercially available software (SPSS IBMS 21 for windows, SPPS IBM, Inc., Chicago, IL).

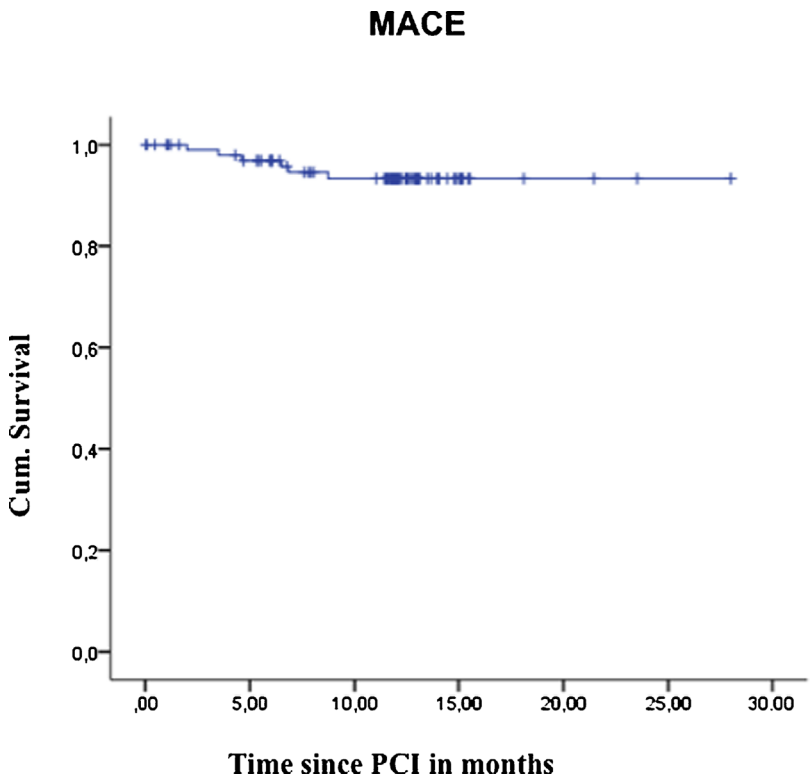

Figure 3. The cumulative survival (CS) free of MACE, by the Kaplan–Meier method, for 6 and 12 months, was 96.9% (95%CI: 93.4–99.8) and 93.3% (95%CI: 88.3–99.2), respectively.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Population. A total of 104 patients were prospectively included in the study. The population (Tables 1 and 2) had a mean age of 65 ± 10 years, 43% were diabetic. Most of the patients (58%) presented with an acute coronary syndrome (ACS). A total of 74% of patients had at least 2-vessel disease and in most of these patients a stent was implanted outside of the target lesion. A total of 42% of lesions-treated lesions with the DEB involved branches of the major epicardial arteries (bifurcated lesion), the first diagonal being the most frequently treated lesion (31%).

Concerning the procedures (Table 3), predilatation was undertaken in all patients with a regular balloon, smaller in diameter and shorter in length than DIOR balloon. The mean DIOR inflation time was around 100 seconds. Reference vessel diameter was 1.95 ± 0.32 mm and final diameter stenosis and acute gain were 23.1 ± 10.2% and 1.05 ± 0.3 mm, respectively (Table 4).

Short- and Long-Term Outcomes. The procedure was angiographically successful in 93% of patients. In 7%, a bailout BMS was required after Dior angioplasty because of coronary dissection more than type B (7 cases). The stent was implanted within the DEB treated zone in all cases. Clinical follow-up at 1 month was available for all patients and no MACE was reported. At a median of 12 (11.1–13.1) months, the cumulative rate of adverse events is given in Table 5. The traditional MACE rate was only 4.8%: cardiac death in 2 (1.9%), any MI in 1 (1.0%), and TLR in 3 (2.9%). The cumulative incidence of MACE is shown in Figure 4. By our definition, 2 cardiac deaths were reported. One was a case of sudden death at 3 months in a patient with 3 vessel disease in which a BMS and DES were also implanted at the time of the index procedure. The other was a case of death of unknown cause at 7 months, in a patient with a 1,0,1 bifurcation lesion involving a first marginal branch treated with DCB.

Angiographic Outcomes. Baseline angiographic analyses confirmed that the lesions treated were located in really small vessels (reference vessel diameter was 1.95 ± 0.32 mm). By protocol

Table 1. Baseline Demographic and Clinical Patients Characteristics, n–= 104

Age, years (mean ± SD)	65.3 ± 10.3
Male gender	(78) 75.0
Risk factors	
Diabetes mellitus	(45) 43.3
Hipertensión	(74) 71.2
Dyslipidaemia	(68) 65.4
Current smoker	(34) 32.7
Renal impairment (creatinine ≥1.5 mg/dl)	(8) 6.7
History of	
Myocardial infarction	(25) 24.0
PCI	(24) 23.1
Coronary bypass surgery	(5) 4.8
Clinical presentation	
Acute coronary syndrome	(60) 57.7
STEMI	(11) 10.6
3 vessel disease	(29) 27.9
≥2 vessel disease	(77) 74.0
LVEF ≤ 50% (mean ± SD)	(27) 32.5

Unless specified otherwise, values are (n) and % of patients. PCI, precutaneous coronary interventions; STEMI, <24 h of ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction.

Table 2. Baseline Lesion Characteristics, n = 104

Small vessel indication	(104) 100
SMV alone	(53) 51.0
SMV + bifucation lesion (001, 111, 011, 101)	(44) 42.3
SMV + contraindication to DAT	(7) 6.7
Target vessel treated	
Fisrt diagonal branch	(33) 31.7
Fisrt Marginal branch	(21) 20.2
Posterior descending artery (RCA)	(11) 10.6
Second Marginal branch	(8) 7.7
Overall bifurcation lesion	(44) 42.3
Type of bifurcation (medina classification)	
111	(22/44) 50.0
001	(11/44) 25.0
101	(5/44) 11.3

Unless specified otherwise, values are (n and %) of patients. SMV, small vessel; DAT, dual antiplatelet therapy; aspirine plus clopidgrel.

Table 3. Baseline Procedural Characteristics, n = 104

Radial approach	(47) 45.2
6-French guide catheter	(85) 81.7
Pts with stent implanted out of the TL	(57) 54.8
DES implanted out of the target lesion	(46) 44.2
Complete revascularization	(64) 61.5
Predilatation (plain balloon)	(104) 100
Balloon diameter mm, (mean ± SD)	2.01 ± 0.3
Balloon length mm, (mean ± SD)	15.8 ± 4.1
Main balloon pressure mmHg, (mean ± SD)	12.2 ± 3.0
Dior balloon angioplasty	(104) 100
Balloon diameter mm, (mean ± SD)	2.2 ± 0.2
Balloon length mm, (mean ± SD)	20.2 ± 5.3
Main balloon pressure mmHg, (mean ± SD)	12.8 ± 3.3
Balloon inflation time second (mean ± SD)	105.5 ± 53.2
Second generation of DIOR	(48) 46.1
Postdilatation after DIOR angioplasty	(6) 5.8
Bail-out indication of bare metal stent	(7) 6.8
Acute recoil (acute stenosis ≥50%)	(0) 0
Coronary disection ≥ type B	(7) 100
Stopped DAT ≤6 months	(9) 8.7
Glycoprotein IIb/IIIa inhibitor	(2) 1.9
Angiographic success	(97) 93.3

Unless specified otherwise, values are (n) and % of patients. Pts, patients; TL, target lesion; DAT, dual antiplatelet therapy; aspirine plus clopidogrel.

angiographic follow-up was mostly undertaken in 2 predefined centers (84%) that was 49.5% respect to the overall population. Angiographic outcomes are shown in Table 4. "In-stent" (in-balloon) late loss was 0.31 ± 0.2 mm, with a binary in-segment restenosis of 19.6% (10).

Table 5. Cumulative Nonhierarchical Major Cardiac Adverse Events (MACE) at 1 and at a Median of 12.0 (11.1–13.1) Months Follow-Up

Follow-Up	1 Month	12 Months
Overall death	(0) 0	(3) 2.9
Cardiac	(0) 0	(2) 1.9
Non-cardiac	(0) 0	(0) 0
Q and nonQ wave MI	(0) 0	(1) 1.0
Target lesion revascularization	(0) 0	(3) 2.9
MACE	(0) 0	(5) 4.8
Stent Thrombosis (ARC)	(0) 0	(1) 1.0

Values are numbers (n) and % of patients. MI, myocardial infarction; MACE, major adverse cardiac events: ARC, academic research consortium.

Predictors of Adverse Events. As is shown in Table 6, at 12 months, by Cox multivariate analysis, independent predictors of adverse events (MACE) were the following: bailout BMS after DEB failure, and STEMI as clinical presentation. Complete revascularization was a protective factor for MACE. Bifurcation lesion type was a predictor of binary restenosis as was stent implantation outside of the target lesion (Fig. 4). The DIOR balloon type (first vs second generation) was not associated with adverse event rate at follow-up.

Discussion

The main finding of this prospective multicenter registry is that PCI for unselected patients treated for small coronary vessel disease using the DIOR

Table 4. Quantitative Angiographic Analysis of Lesions Treated With Angiographic Follow-Up at a Mean of 7.5 ± 2.6 Months (n = 51 Lesions; 83.6% of Angio FU Completed in 2 Centers, and 49.5% of the Overall Population)

N = 51 (39.3% 1st G of DIOR)	Preangioplasty	Postangioplasty	Angio FU
Reference diameter, mm	1.95 ± 0.32		
Lesion length, mm	12.8 ± 7.1		
MLD, mm	0.49 ± 0.28	1.54 ± 0.34	1.23 ± 0.53
Diameter stenosis, %	76.8 ± 13.4	23.2 ± 10.2	39.7 ± 26.1
Acute gain, mm		1.05 ± 0.3	
Late luminal loss, mm			0.31 ± 0.2
Binary restenosis, n (%)			(10) 19.6

Unless specified otherwise, values are mm, (mean ± SD). MLD, minimum luminal diameter.

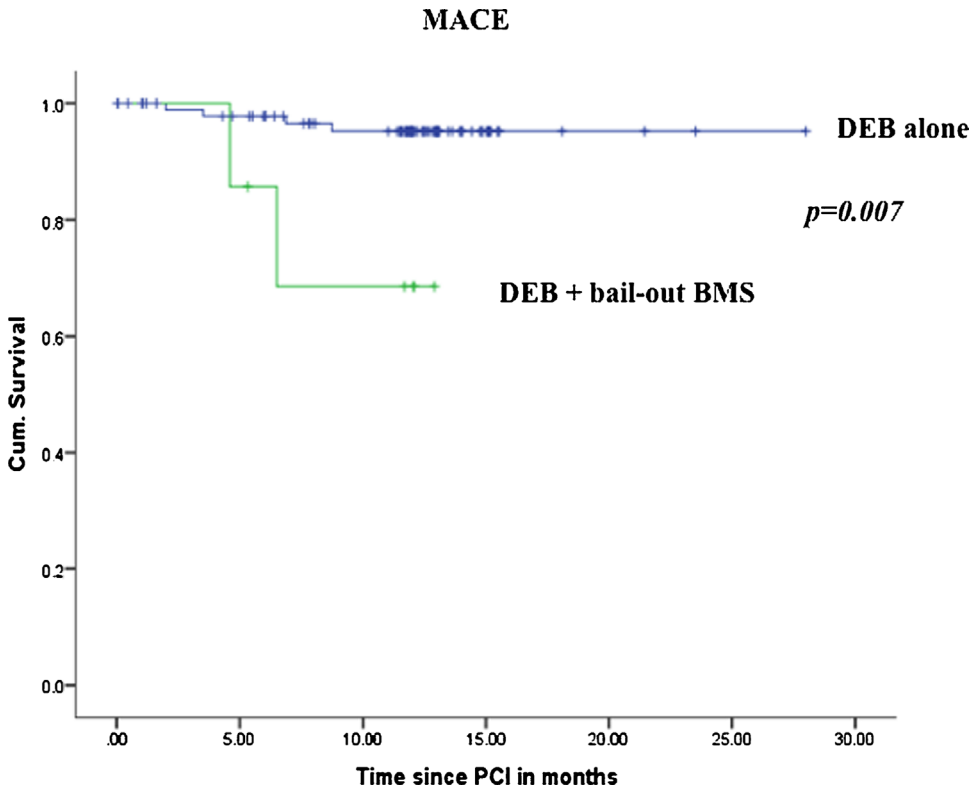

Figure 4. The cumulative survival (CS) free of TLR, by the Kaplan–Meier method, comparing "the combined strategy" DEB plus bailout-BMS versus DEB as stand alone therapy. Mean survival time free of TLR was 10.6 (7.9–13.3) versus 26.9 (25.8–27–9.5) months, P = 0.007, respectively.

paclitaxel-coated DEB is associated with excellent immediate and longer term results (1-year MACE of 5% with TLR 3% and 7 months late loss of 0.3 mm). This "real-world" registry is unique in including a significant group of symptomatic patients (70% ACS) with only one target lesion located in a really small vessel; a significant proportion of treated lesions involving branches of the major epicardial arteries (42%). An additional finding is that the group of patients treated with DCB plus additional bailout BMS

Table 6. At 12 Months, We Found by Cox Multivariate Analysis That the Significant Predictor of Adverse Event Were as Shown Below

MACE	HR	IC 95%	P-Value
DEB + Bailout BMS	18.74	2.58–135.84	0.004
STEMI	9.99	1.40–71.18	0.022
Complete Revascularization	0.10	0.01–0.87	0.038
TLR			
DEB + Bailout BMS	30.99	2.79–344.07	0.005
Restenosis			
Pts with stent implanted out of the TL	9.439	1.19–74.72	0.03
Bifurcated lesion	6.707	0.84–53.16	0.07

implantation had a significantly worse outcome than those treated with DCB alone. We found that bailout-BMS after DEB angioplasty was an independent predictor of MACE and TLR. A bigger Dior balloon diameter was related with DEB failure and bail-out BMS. Predictably STEMI as a clinical presentation predicted MACE and treatment of bifurcartions was associated with restenosis.

Small vessel disease has been defined as lesions involving coronary arteries with a diameter of <3 mm by visual estimation. The definition includes a wide range of vessel diameters but this is based on the lack of benefit of BMS over with balloon angioplasty in vessels less than 3 mm.[1,24] Vessel size is inversely correlated with the risk of restenosis and adverse outcome after percutaneous coronary interventions. This is because the amount of neointimal hyperplasia is largely independent of vessel size, and thus, small vessels are more prone to restenosis than larger vessels because they are less able to accommodate neointimal tissue without compromising blood flow.[5,6] In this paper, we report results in patients with mean reference diameter by visual estimation $\leq$2.25 mm. Compared with trials which include lesions placed in small vessel ($<$2.8 mm), we report the lowest rate of MACE (5%) and TLR (3%) at 1 year.[3,17,19,24] Moreover, DEB also could provide a therapeutic option in very small vessels ($<$2.25 mm), for which DES sizes are not available.

In the ISAR SMART trial, Castrati et al. reported for POBA group (n = 200) a late luminal loss of 0.72 ± 0.71mm, with binary stent restenosis of 31.4% and TLR of 20.1% at 6–7 months, similar results were described for the BMS group (n = 204).[24] In the randomized trial, ISAR-SMART 3, comparing paclitaxel (PES) (n = 180) versus sirolimus-eluting stents (SES) (n = 180), they reported better late loss, restenosis, and TLR results for SES group (0.25 ± 0.55 vs 0.56 ± 0.59 mm), (11.4 vs 19.0%), and (6.6 vs 14.7%), respectively.[3]

Regarding trials using DEB technology, the PEP-CAD I (n = 118) was the first study (single-arm nonrandomized trial) evaluating the safety and efficacy of the Sequent Please balloon for the treatment of small vessel disease (mean reference diameter 2.35 ± 0.19 mm), and showed good angiographic (late loss of 0.28 ± 0.53 mm) and clinical results at 12 months (TLR of 4.9%), thus, demonstrating that DEB possibly yields the potential as treatment alternative for these types of lesions.[17] Two randomized trials have reported different results. The published BELLO randomized trial reported that the In.Pact Falcon DEB (n = 94) was noninferior to PES (n = 97) in suppressing neointimal proliferation in small vessels. Furthermore, DEB and PES were associated with similar rates of angiographic restenosis (10.0 vs 12.6%), late loss (0.08 ± 0.38 vs 0.29 ± 0.44 mm), and repeat revascularisation (4.4 vs 7.6%).[19,25] On the other hand, the PICCOLETO trial failed to demonstrate DIOR I DEB equivalence to a PES for the treatment of small vessel disease, both in terms of angiographic and clinical restenosis. It is important to note some procedural limitations of this study as plain balloon predilatation was done only in 25% of cases and bailout stent implantation in the DEB group was 35.6% with the occurrence of so-called "geographical mismatch," which led to restenosis in stented lesion sites that were not adequately pretreated with DEB.[18]

In our trial we were particularly careful to use DCB as a delivery drug system, thus lesion predilatation was performed in all cases with a shorter plain balloon than DIOR. Thus, bailout stent implantation was only needed in 7.5% of cases, and in these cases investigators were particularly careful to ensure that any needed stent was implanted within the DEB-treated zone. We found that bailout BMS implantation was a strong predictor of MACE and TLR. Moreover, we reported, that a bigger mean diameter of the DIOR balloon (2.36 ± 0.13 vs 2.18 ± 0.23 mm, P = 0.048) was related with higher rate of bailout BMS implantation. The main reason of DEB failure was dissection and mean reference diameter. Thus, probably, the mean diameter of the DIOR balloon used in the DEB plus BMS (failure group) was over sized. According to this, the PEPCAD I, reported a significantly higher late loss and restenosis rate in lesions treated with a combination of DEB and bail-out BMS, especially if geographic mismatch occurred (i.e. stent implanted in an area that was not treated with DEB).[17] Thus, when using DCB the technique and method of usage is important and may have a clinical impact on the results.

Limitations of the Study. Because of the exploratory nature of this study, no "a priori" sample size was calculated. In this real-world registry CPKs were only drawn if patients were having ongoing chest pain and/or ECG changes, thus the rate of MI and MACE was probably underestimated. The smaller mean reference vessel size compared with other trial using similar technology could explain the relative higher rate of angiographic restenosis but at the same time as

TLR was symptom or ischemia driven, the rate of TLR might be lower compared to some trials with bigger vessel reference diameter.

Conclusion

Percutaneous intervention for unselected patients treated for small coronary vessel disease ($\leq$2.25 mm) using the DIOR, paclitaxel-coated balloon, with a predefined strategy is associated with excellent immediate and long-term results. However, drug-coated balloon technology cannot overcome the mechanical limitation of acute recoil and flow-limiting dissections seen sometimes after balloon angioplasty. The bailout BMS after drug-coated balloon failure is clearly inferior to drug-coated balloon as stand alone therapy.

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