Original article

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Treatment of coronary artery disease with a new-generation drug-coated balloon: final results of the Italian Elutax SV rEgistry-DCB-RISE

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Aims **Drug-coated balloons (DCBs) are a recognized alternative to stents for the treatment of in-stent restenosis (ISR), and there is some initial clinical evidence about their efficacy for the treatment of small coronary vessels. Newer-generation DCBs were developed to overcome the reduced deliverability of the previous generation, also warranting a more effective drug delivery to vessel wall. However, the vast majority of new-generation DCBs still lack of reliability due to paucity of clinical data.**

Methods **Between 2012 and 2015, all patients treated with Elutax SV DCB (Aachen Resonance, Germany) at nine Italian centers were enrolled in this retrospective registry. Primary outcome was the occurrence of target-lesion revascularization (TLR) at the longest available follow-up. Secondary endpoints were procedural success and occurrence of device-oriented adverse cardiovascular events including cardiac death, target-vessel myocardial infarction, stroke, and TLR. A minimum 6-month clinical follow-up was required.**

Results **We enrolled 544 consecutive patients treated at 583 sites. Fifty-three per cent of the patients had ISR, and the rest native vessel coronary artery disease. Procedural success occurred in 97.5%. At the longest available clinical follow-up (average 13.3 ± 7.4 months), 5.9% of the patients suffered a TLR and 7.1% a device-oriented adverse cardiovascular event. We did not register cases of target-vessel abrupt occlusion. At multivariate analysis, severe calcification at the lesion site was the first determinant for the occurrence of TLR.**

Conclusion **This registry on the performance of a new-generation DCB shows an adequate profile of safety and efficacy at mid-term clinical follow-up.**

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Keywords: clinical registry, drug-coated balloon, target-lesion revascularization

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Introduction

In recent years, drug-coated balloons (DCBs) have emerged as a therapeutic option in the interventional field.[1,2] Preliminary data showed how DCBs were a valuable treatment strategy in case of in-stent restenosis (ISR), either of bare-metal stent (BMS) or drug-eluting stent (DES).[3–6] Later, DCBs have also been used for the treatment of native coronary vessel disease as an alternative to DES in selected cases.[7] Several paclitaxel-coated balloons were released and obtained the european community mark, with different behavior and outcome, so that a 'class effect' does not exist for this technology. Recent advances, both in terms of device deliverability and effective drug release, and retention led to the creation of the arbitrary names 'second-' or 'latest-generation' DCBs. To this day, the clinical outcome of any of this newer 'generation' of DCBs is not available yet. With the drug-coated balloon- Results of the Italian elutax SV registry (DCB-RISE), we aim to investigate the clinical performance of one of these devices.

Methods

We here report the main results of the DCB-RISE registry, an investigator-initiated, retrospective, all-comer real-world registry of patients who were treated with the Elutax SV (Aachen Resonance, Germany) DCBs. The aim of this registry was to assess the safety and efficacy of Elutax SV at the longest available clinical follow-up. This study was not funded and ethically approved.

Study procedure

All patients underwent percutaneous coronary intervention (PCI) following international guidelines[8,9] and according to local practice. Antithrombotic treatment

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was left at the operator's discretion, with a minimum of 30-day dual antiplatelet therapy (DAPT), that was increased to a minimum of 3 months in case of additional stent implantation, or more based on the clinical indication (e.g. acute coronary syndrome).

Stent implantation after DCB use was discouraged, unless a major dissection (>type B) or vessel recoil was discovered after PCI. In this case, DES use was suggested unless contraindicated. Avoidance of geographical mismatch was also recommended (in case of stenting the prosthesis had to be placed within and not exceeding the area previously treated with DCBs). Finally, in order to avoid acute recoil, we also suggested to wait for at least 10 min after DCB inflation before ending the intervention.[9]

After the procedure patients were clinically followed, according to the local practice.

Device

The device tested in this study is a rapid exchange percutaneous transluminal coronary angioplasty balloon catheter. Once inflated, it delivers the drug it is coated with to the vessel wall. The balloon is coated with an active pharmaceutical agent for preventing restenosis: 2.2 μg paclitaxel mm^{-2} with a tolerance of 1.4–3.00 μg paclitaxel mm^{-2} and has a 0.7 μg dextran mm^{-2} top coating with a maximum amount of 1.89 μg dextran mm^{-2}, which acts as excipient (drug carrier). The functional characteristic of the formulation is to release paclitaxel to the tissue of the vascular wall during inflation and to maintain it during the first days. The uptake of paclitaxel is controlled by the interaction with dextran and the vessel wall. The drug uptake measured in different animal models is highest after 1 h and decreases slowly over days and weeks, with values of around 250 μg ml^{-1} decreasing to around 100 μg ml^{-1} after 1 week to 10 μg ml^{-1} after 4 weeks, allowing a successful inhibition of proliferation and migration of smooth muscle cells over time.

Study endpoints

The primary endpoint was the occurrence of target-lesion revascularization (TLR) at the longest available follow-up. Secondary endpoints were procedural success, defined as angiographic success in the absence of in-hospital complications, and the occurrence of a device-oriented endpoint [device-oriented adverse cardiovascular event (DOCE)], which included cardiac death, target-vessel myocardial infarction (MI), stroke, or TLR.

Angiographic success was defined as Thrombolysis in Myocardial Infarction 3 flow with <50% final stenosis at the end of intervention. MI was defined according to the universal definition[10] and was considered only in case it was spontaneous. TLR was defined as repeat PCI or coronary artery bypass grafting for the target segment or within 5 mm proximally or distally.

Table 1 Baseline patient characteristics

Variable	$n = 544$
Demographic characteristics	
Age years, mean ± SD	67.25 ± 10.7
Male sex	388 (71%)
Cardiovascular risk factors	
Hypertension	413 (76%)
Diabetes	177 (32%)
Smoking history	217 (40%)
Previous myocardial infarction	228 (42%)
Previous bypass surgery	70 (13%)
Clinical characteristics	
LV ejection fraction, mean ± SD	53.3 ± 9.6
Chronic kidney disease (eGFR <30 ml min^{-1})	72 (13%)
Clinical presentation	
UA (troponine negative)	53 (9.7%)
NSTEMI	202 (37%)
STEMI	24 (4.4)
Stable CAD	265 (48.7)

Data are mean ± SD or *n* (%). ACS, acute coronary syndrome; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; LV, left ventricle; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Statistical analysis

Categorical variables are reported as count and percentage, whereas continuous variables as mean and standard deviations or interquartile range (IQR). Gaussian or not Gaussian distribution was evaluated by Kolmogorov–Smirnoff test. The *t* test has been used to assess differences between parametric continuous variables, Mann–Whitney *U* test for nonparametric variables, the chi-square test for categorical variables, and Fisher's exact test for 2×2 tables. Cox multivariate analysis was performed to assess the independent predictors of TLR, including all variables, which differ at univariate analysis or with significant association with TLR.

Proportional hazards assumption was not violated in statistical analysis. A two-sided *P* value less than 0.05 was considered statistically significant; all analyses were performed with SPSS 21.0 (IBM, Armonk, New York, USA).

Results

All consecutive patients treated with Elutax SV at nine Italian centers between December 2012 and December 2015, and with at least 6 months clinical follow-up available, were included in the DCB-RISE registry. In all, 544 patients (age 67 ± 12 years) with 583 lesions were included. One hundred and seventy-seven (32.6%) patients had diabetes mellitus, and 13% had chronic kidney disease with estimated glomerular filtration rate below 30 ml min^{-1}. In 49% of the patients, the clinical indication for PCI was stable coronary artery disease, and 4% of the population had a ST-elevation MI caused by ISR. Table 1 describes the clinical characteristics of the population.

Table 2 Angiographic and procedural characteristics, discharge

Variable (lesions treated with DCB)	583
Target vessel	
Left anterior descending artery	274 (47%)
Left circumflex artery	102 (17%)
Right coronary artery	190 (33%)
Saphenous vein graft	23 (4%)
Arterial graft	5 (0.9%)
Number of diseased vessels	
One-vessel	281 (48%)
Two-vessels	169 (29%)
Three-vessels	124 (21%)
Graft disease	9 (1.5%)
In-stent restenosis	
ISR after BMS	114 (19%)
ISR after DES	189 (32%)
Native vessel disease	280 (48%)
Lesion involving bifurcation with SB >2 m	96 (16.5%)
CTO	20 (3.4%)
Severe calcifications	19 (3.3%)
Moderate calcifications	62 (11%)
QCA analysis	
Lesion length, mm ± SD	16.9 ± 7.2
Long lesions (>24 mm)	88 (15%)
RVD, mm ± SD	2.84 ± 1.18
Preprocedural MLD, mm ± SD	0.43 ± 0.31
Percentage diameter stenosis pre, % ± SD	85.0 ± 11.4
Lesion preparation	
Absence of lesion predilatation	49 (8.4%)
Predilatation with semicompliant balloon	380 (65%)
Predilatation with noncompliant balloon	189 (32%)
Predilatation with scoring balloon	14 (2.4%)
Diameter of predilatation balloon, mm ± SD	2.9 ± 0.67
Number of DCB used/lesion, *n* ± SD	1.3 ± 0.63
DCB diameter, mm ± SD	2.9 ± 0.49
DCB length, mm ± SD	20.5 ± 6.47
DCB inflation, atmospheres ± SD	11.0 ± 3.9
DCB inflation length, s ± SD	55.6 ± 26.4
Stent implantation after DCB PCI	
DES implantation	62 (11%)
BVS implantation	1 (0.2%)
BMS implantation	4 (0.7%)
Final MLD, in segment, mm ± SD	1.57 ± 0.39
Final percentage diameter stenosis, % ± SD	17 ± 11.5
Angiographic success	576 (98.7)
Procedural failure	7 (1.3%)
IVUS/OCT use	60 (10%)
GP IIb/IIIa Inhibitors	21 (3.6%)
Bivalirudin use	2 (0.3%)
Aspirin at discharge	536 (98%)
Clopidogrel at discharge	410 (75%)
Ticagrelor at discharge	39 (7.2%)
Prasugrel at discharge	14 (2.6%)

ACS, acute coronary syndrome; BMS, bare-metal stent(s); BVS, bioresorbable vascular scaffold; CAD, coronary artery disease; DCB, drug-coated balloon; DES, drug-eluting stent(s); FFR, fractional flow reserve; GP, glycoprotein; IVUS, intravascular ultrasound; MLD, minimal lumen diameter; OCT, optical coherence tomography; TIMI, Thrombolysis in Myocardial Infarction.

Drug-coated balloon was used predominantly to treat ISR, either DES (32.4%) or BMS (19.5%) restenosis. On the contrary, treatment of de-novo coronary artery disease occurred in 48.1% of the patients, including 16.5% of patients with bifurcation with greater than 2 mm side branch diameter.

Average lesion length was 16.9 ± 7.2 mm and reference vessel diameter 2.84 ± 1.18 mm. According to study and consensus paper recommendations,[9] only less than 10% of the lesions were directly treated with DCBs, whereas the vast majority was pretreated either with semicompliant or noncompliant balloons. The average DCB length was 20.5 ± 6.47 mm, with an average diameter of 2.9 ± 0.49 mm. Stenting after DCB was required in 12.3% of the patients. In seven cases (1.3%), the procedure failed because it was impossible to reach the target lesion with the device, and the procedure was converted to DES-PCI (two cases) or plain-old balloon angioplasty (five cases). Procedural success occurred in 97.5% of the cases.

Table 3 Clinical endpoints at the longest follow-up available

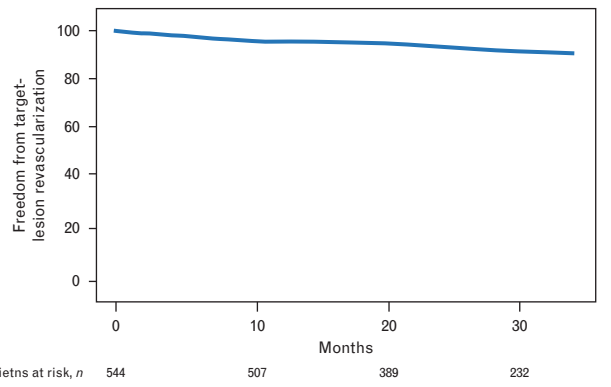
Variable	*n* = 507
Duration of follow-up, months, average (SD)	13.3 (7.4%)
TLR	30 (5.9%)
TLR managed with CABG	4 (0.8%)
TLR managed with PCI	26 (5.1%)
Acute vessel occlusion	0
Target vessel MI	3 (0.6%)
Stroke	2 (0.4%)
All-cause death	12 (2.4%)
Cardiac death	3 (0.6%)
DOCE	36 (7.1%)
TVR (non-TLR)	12 (2.4%)

CABG, coronary artery bypass graft; DOCEs, device oriented cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TVR, target vessel revascularization.

Dual antiplatelet therapy was prescribed in 452 patients (83.1%) at discharge, and was prolonged for 1 month in 432 of them (79.4%); at final follow-up, only 39 patients (6.4%) were still on DAPT. Table 2 describes the angiographic and procedural characteristics of the population.

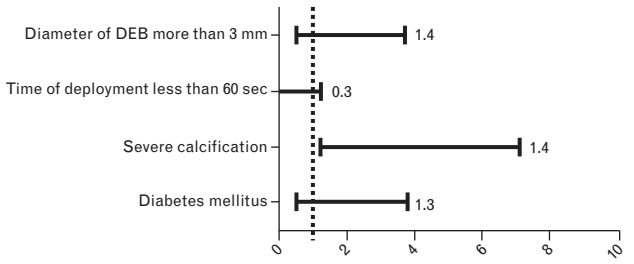
Average clinical follow-up was 13.3 ± 7.4 months and was available for 507 (93.2%) patients. Table 3 describes the main study results. The primary outcome measure, TLR, was observed in 30 (5.9%) patients. TLR was managed with coronary artery bypass graft in four patients (0.8%) and with re-PCI in 26 patients (5.1%) (Fig. 1). DOCE, secondary study endpoint, occurred in 36 (7.1%) patients. Cardiac death or MI occurred in 3 patients (0.6%),

Fig. 1



Kaplan–Meier curve of survival from the primary study endpoint, TLR, at the longest available follow-up. TLR, target-lesion revascularization.

Fig. 2



Multivariate analysis with independent predictors for TLR. TLR, target-lesion revascularization.

whereas all-cause death occurred in 12 patients (2.4%). Cerebrovascular stroke occurred in two patients (0.4%).

Multivariate analysis showed that only severe calcifications at lesion site were an independent predictor of TLR (Figs 2 and 3).

We undertook a subanalysis of the data comparing patients treated for ISR and patients treated for de-novo lesions, and observed a significant difference in the TLR rate that occurred in 9 vs. 2.6% ($P = 0.006$), respectively; DOCEs were significantly higher in the ISR group (11 vs. 2.6%; $P = 0.001$), whereas no significant statistical difference was observed in terms of cardiac death, target vessel myocardial infarction, and stroke (Table 4). TLR rate was not different between patients with BMS or DES-ISR.

Table 4 Clinical endpoints at the longest available follow-up

	$n = 507$		
	13.3 (7.4)		
Average duration of follow-up, months (SD)	ISR ($n = 269$)	*de novo* ($n = 238$)	*P*
TLR, *n* (%)	24 (9%)	6 (2.6%)	0.006
TLR managed with CABG, *n* (%)	3 (1%)	1 (0.4%)	0.64
TLR managed with PCI, *n* (%)	21 (7.8%)	5 (2.1%)	0.003
Target-vessel MI, *n* (%)	3 (1.1%)	0	0.14
Stroke, *n* (%)	1 (0.3%)	1 (0.4%)	1
All-cause death	6 (2.2%)	6 (2.5%)	0.36
Cardiac death	3 (1.1%)	0	0.27
DOCE	30 (11%)	6 (2.6%)	0.001

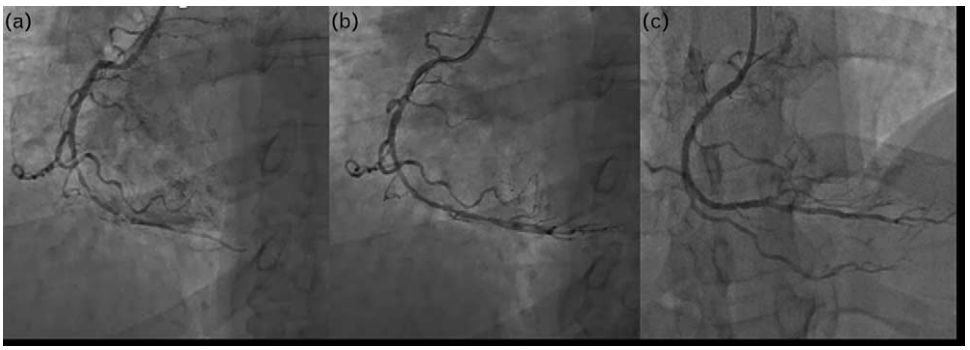
CABG, coronary artery bypass graft; DOCE, device-oriented cardiovascular events; ISR, in-stent restenosis; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target-lesion revascularization.

Discussion

The study shows how a PCI performed with one of the latest-generation DCBs is feasible and well tolerated at mid-term follow-up, with a low rate of TLR, also taking into consideration the medium/high-risk profile of the population (half of the patients had ISR as indication for PCI). This endpoint is also similar to the one observed in a registry with one of the most widely used DCB, at a shorter follow-up.[11] In another registry, a different DCB showed similar results in terms of safety and efficacy after 12 months.[12] In the international, multicenter, prospective, all-comers SeQuent Please World Registry,[13] a real-world registry which included both patients treated for ISR and de-novo lesions, the TLR rate was 5.2%, similar to the one observed in our registry; moreover, also analyzing the outcomes in native coronary lesions, TLR rates were comparable in the twio registries (respectively, 2.4 and 2.6%).

The main potential advantages of DCBs are as follows: a quick and homogeneous release of the antiproliferative drug to the vessel wall, which is absorbed and has a prolonged effect, attenuating the process of neointimal hyperplasia; the absence of polymer, which can reduce or eliminate the vascular inflammatory response, which is directly linked to late thrombotic events; the absence of a metal platform; the need for shorter DAPT. The role of DCB has recently gained a precise role in interventional cardiology, being the first choice for the treatment of DES or BMS restenosis in many centers. The DCB role

Fig. 3



(a) Chronic total occlusion of the right coronary artery (RCA). (b) Final angiographic result after angioplasty with a 2.5/30 mm Elutax SV drug-coated balloon, with persisting 30–40% stenosis. (c) Six-month angiographic follow-up, showing good persisting patency of the RCA and visible vessel lumen gain.

for the treatment of native coronary vessels is less recognized and these devices are less widely used in this setting, but some preliminary studies show interesting data in terms of vessel dissection healing and late coronary lumen gain, although prospective studies on the matter are still lacking.[7,14,15] Current patients treated in the cath laboratories of western countries represent a highly complex population with frequent involvement of two or three coronary vessels, diffuse disease, and small vessels. These anatomical settings seem appropriate for a hybrid strategy that can reduce the total stent length, thus may potentially reduce the risk for late adverse events. Our study also confirms how DCBs may constitute a reasonable addendum to DES in diffuse coronary disease, as some preliminary data have previously shown. In this study, 38% of the entire population underwent an all-in-one (21%) or staged (17%) hybrid procedure,[16] and the outcome between hybrid or solo-DCB PCI did not differ.

On the contrary, one potential advantage of a solo-DCB PCI is the possibility to reduce the duration of DAPT. The recently published european society of cardiology 2017 update document on DAPT[17] acknowledges the lack of dedicated clinical trials investigating the optimal duration of DAPT in patients treated with DCBs and recommends a DAPT duration of 6 months (class IIa, B); it must be noted, though, that in the largest randomized trials,[18,19] a 3–12-month DAPT duration was recommended, whereas real-world registries[13] suggest a duration of at least 1 month. In our clinical practice, we follow the recommendations of current consensus documents that suggest 30 days after DCB use for native vessels, and 3–6 months in case of stent implantation.[9] However, the possibility to reduce it further, or even discharge the patient with one single antiplatelet, seems intriguing. In the registry, 17% of the patients did not receive the second antiplatelet at discharge, the main reasons being the need for elective/urgent surgery (6%) or recent bleeding or high risk of bleeding (9%). To note, a subanalysis of the cohort of patients discharged with one single antiplatelet showed clinical results similar to the rest of the population, theoretically suggesting a role for this strategy in a highly selected patient population.

A specific mention should be made on the device used in this study. Preliminary results with the first generation of DCBs showed how these devices are different in terms of efficacy, and underlined the importance of a drug carrier, firstly with the role of targeting paclitaxel to the lesion site (a sort of protection from proximal tortuosities and disease), and then, after balloon inflation, to help the drug to reach the vessel wall and persist there. In the recent years, all new generations of DCBs were developed with dedicated carriers, and both randomized controlled studies and real-world registries showed their good efficacy and no specific safety issue. The Elutax SV DCB tested in this registry has already shown to warrant adequate late lumen loss at 6-month angiographic follow-up.

There are several limitations that need to be acknowledged for the current registry. There was not data monitoring, and clinical event assessment was performed by the single investigators. The absence of a prospective enrollment is another major limitation, for example, it was not possible to know the reasons why operators preferred a DCB over a DES at index procedure, and device selection might have suffered of unknown confounders. Also, there was not a direct comparison with 'old-generation' DCBs. Periprocedural MI was not an endpoint, and only spontaneous MIs were collected.

In conclusion, the DCB-RISE registry shows how the use of the new-generation DCB Elutax SV in an all-comer population is associated with good mid-term clinical outcome, which is comparable with other similar devices present in the market.

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Effect of Drug-Coated Balloons in Native Coronary Artery Disease Left With a Dissection

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ABSTRACT

OBJECTIVES The authors sought to understand the clinical and angiographic outcomes of dissections left after drug-coated balloon (DCB) angioplasty.

BACKGROUND Second-generation DCB may be an alternative to stents in selected populations for the treatment of native coronary lesions. However, the use of these devices may be hampered by a certain risk of acute vessel recoil or residual coronary dissection. Moreover, stenting after DCB has shown limited efficacy. Little is known about when a non–flow-limiting dissection is left after DCB angioplasty.

METHODS This was a prospective observational study whose aim was to investigate the outcome of a consecutive series of patients with native coronary artery disease treated with second-generation DCB and residual coronary dissection at 2 Italian centers. We evaluated patient clinical conditions at 1 and 9 months, and angiographic follow up was undertaken at 6 months.

RESULTS Between July 2012 and July 2014, 156 patients were treated with DCB for native coronary artery disease. Fifty-two patients had a final dissection, 4 of which underwent prosthesis implantation and 48 were left untreated and underwent angiographic follow-up after 201 days (interquartile range: 161 to 250 days). The dissections were all type A to C, and none determined an impaired distal flow. Complete vessel healing at angiography was observed in 45 patients (93.8%), whereas 3 patients had persistent but uncomplicated dissections, and 3 had binary restenosis (6.2%). Late lumen loss was 0.14 mm (−0.14 to 0.42). Major adverse cardiovascular events occurred in 11 patients in the entire cohort and in 4 of the dissection cohort (7.2% vs. 8.1%; p = 0.48). We observed 8 and 3 target lesion revascularizations, respectively (5.3% vs. 6.2%; p = 0.37).

CONCLUSIONS In this cohort of consecutive patients treated with new-generation DCB and left with a final dissection, this strategy of revascularization seemed associated with the sealing of most of dissections and without significant neointimal hyperplasia. (J Am Coll Cardiol Intv 2015;8:2003–9) © 2015 by the American College of Cardiology Foundation.

Drug-coated balloons (DCB) were developed to overcome neointimal hyperplasia and have been widely tested for the treatment of in-stent restenosis, in which setting they have shown an efficacy comparable to drug-eluting stents (DES) in terms of target lesion revascularization (TLR) (1–4). For this indication, DCB gained a Class I, Level of Evidence: A in the latest European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines for myocardial revascularization (5).

However, from the mechanical point of view, DCB behave just like simple balloons, thus they share some of the main limitations of these devices after angioplasty, namely coronary dissection and acute recoil.

Very preliminary observations seem to show how new-generation DCB could be associated with a faster spontaneous healing of an arterial dissection left after balloon angioplasty, especially in case of angioplasties of the femoropopliteal region and for the treatment of in-stent restenosis (6,7). The aim of this study was to test this hypothesis in a consecutive series of patients with native coronary vessel disease.

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ABBREVIATIONS AND ACRONYMS

DCB = drug-coated balloon(s)

DES = drug-eluting stent(s)

LLL = late lumen loss

MACE = major adverse cardiac event(s)

MLD = minimal lumen diameter

PCI = percutaneous coronary intervention

RVD = reference vessel diameter

TLR = target lesion revascularization

METHODS

This is an observational study conducted at 2 centers expert in DCB angioplasty. The aim of the study was to investigate the outcome of consecutive coronary dissections left after DCB angioplasty in native vessels.

SEE PAGE 2010

Inclusion criterion was any percutaneous coronary intervention (PCI) performed with DCB in native coronary vessels. Exclusion criteria were any use of DCB for reasons different from the aforementioned (e.g., for in-stent restenosis); ST-segment elevation myocardial infarction that occurred in the previous 48 h; or life expectancy <1 year. Other clinical indications for PCI, unstable hemodynamics at presentation, and the presence of renal insufficiency were not exclusion criteria. We had a restrictive use of DCB in case of big vessel size (e.g., >3 mm in diameter) or in case of very calcific vessels, especially when we feared possible vessel recoil.

In the current study, the following devices were used: Restore (Cardionovum, Milano, Italy) and Elutax SV (Aachen Resonance, Lainate, Italy) DCB. These 2 devices, both eluting paclitaxel, may be considered a second-generation DCB because of a more efficient delivery of paclitaxel to the vessel wall, which results in a longer persistence of the drug. Restore DCB has a concentration of paclitaxel of 3.0 μg/mm^2 of balloon surface, and shellac is used as a carrier. Elutax SV DCB has a concentration of paclitaxel of 2.2 μg/mm^2 of balloon surface, and is embedded in a 3-layer matrix. Available measures for both devices used in this study included diameters of 2.0, 2.5, and 3.0 mm, and lengths of 15, 20, 25, and 30 mm.

The intervention was performed according to international guidelines and the recent Italian position paper on DCB PCI (8). Specifically, pre-dilation with an undersized semicompliant balloon was mandatory (the recommended size was 0.9:1 of DCB). In case of flow-limiting dissection after pre-dilation, we recommended considering conversion to a stent PCI without using a DCB. The DCB was inflated for 30 to 45 s at nominal pressure, according to the morphological characteristics of the lesion (e.g., degree of calcification, length, tortuosity). After DCB use, final assessment was undertaken after at least 5 min, in order to catch early vessel recoil. In this event, bailout stent implantation was considered. The type of stent or scaffold was left to the operator's discretion.

Patients with any residual coronary dissection after DCB use entered the current analysis. It is our habit not to stent coronary dissections of type A to C (National Heart, Lung, and Blood Institute [NHBLI] classification system for intimal tears, developed by the Coronary Angioplasty Registry) with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. In case of coronary dissections of type D or higher and/or impaired distal flow, it is our habit to implant a stent.

After sheath insertion, all patients were administered unfractionated heparin (single bolus of 5,000 IU, then adjunctive boluses following activated clotting time) or bivalirudin (bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure). A bailout glycoprotein IIb/IIIa receptor inhibitor strategy was allowed in case of high thrombus burden. All patients received aspirin (either 100 mg/day for at least 3 days before PCI or with a pre-PCI 300-mg intravenous bolus), and clopidogrel (300 or 600 mg as a loading dose, followed by 75 mg daily) or prasugrel (60 mg as a loading dose, followed by 10 mg daily) or ticagrelor (180 mg as a loading dose, followed by 90 mg twice a day) following clinical indication. The duration of prescribed dual antiplatelet treatment was 1 month, or 6 months in case of stent implantation; after this time, patients were prescribed only aspirin.

Angiographic success was defined as a final residual stenosis <50% by visual estimate, with TIMI flow

TABLE 1 Patients' Clinical Characteristics

	All DCB Population, Native Vessels (N = 156)	No Dissection Cohort (n = 104)	Dissection Cohort (n = 52)	p Value
Age, yrs	61 (54–67)	59 (51–64)	60 (54–66)	0.18
Female	50 (32.0)	31 (29.8)	19 (36.5)	0.31
Hypertension	91 (58.3)	59 (56.7)	32 (63.5)	0.21
Hypercholesterolemia	95 (60.9)	65 (62.5)	30 (57.7)	0.32
Diabetes	55 (35.2)	37 (35.6)	18 (34.6)	0.86
Prior MI	14 (9.3)	10 (9.6)	4 (8.4)	0.48
Prior revascularization	17 (10.9)	9 (8.7)	8 (13.5)	0.16
Multivessel coronary disease	78 (50)	52 (50)	26 (50)	0.91
Stable angina	82 (52.6)	55 (52.9)	27 (51.9)	0.84
Unstable angina	31 (19.9)	19 (18.3)	12 (23.0)	0.33
Non-ST-segment elevation MI	43 (27.6)	30 (28.8)	13 (25)	0.75
Culprit vessel				
Left anterior descending artery	88 (56.4)	52 (50)	35 (67.0)	**0.02**
Left circumflex artery	13 (8.3)	10 (9.6)	3 (5.8)	0.06
Right coronary artery	55 (35.2)	42 (40.4)	14 (26.9)	0.842

Values are median (interquartile range) or n (%). p Value in **bold** have reached statistical significance.

DCB = drug-coated balloon; MI = myocardial infarction.

grade 3. Procedural success was defined as angiographic success without the occurrence of in-hospital major adverse cardiac events (MACE) (defined as any occurrence of ST-segment elevation acute myocardial infarction, target vessel revascularization, TLR, or death). Periprocedural myocardial infarction was defined as a post-procedural increase in cardiac troponin T >5 × 99th percentile of the upper reference limit.

All patients underwent clinical follow-up after 1 and 9 months; all patients in the dissection cohort underwent angiographic follow-up with quantitative coronary assessment after 6 months, in order to assess the degree of coronary dissection healing. All measurements were performed on cineangiograms recorded after 200 mg of intracoronary nitroglycerin administration. Identical projections were used for each comparison. Quantitative analysis of angiographic data were initially assessed by a single experienced investigator, and afterwards validated by an internal committee of experts, using the CAAS II research system (Pie Medical Imaging, Maastricht, the Netherlands). The following parameters were analyzed: reference vessel diameter (RVD), minimal lumen diameter (MLD), percent diameter stenosis (the difference between RVD and MLD divided by RVD), late lumen loss (LLL) (defined as the difference between MLD after index PCI and MLD at angiographic follow up), lesion length, binary restenosis, and persistence of dissection (NHBLI classification). Measurements included the whole segment treated plus 5 mm proximally and distally. Binary restenosis was defined as stenosis of at least 50% of the luminal diameter at angiographic follow-up.

Primary endpoint of this study was the percentage of dissection healing detected at angiographic follow-up. Secondary endpoints included TLR, binary restenosis, LLL, and the occurrence of MACE.

Data are presented as mean ± SD or median (interquartile range) as appropriate for continuous variables, and as proportions (%) for dichotomous variables. The differences between groups were assessed by chi-square test or Fisher exact test for categorical data, and paired Student *t* test for continuous data. The relative risk and its 95% confidence interval were calculated for each study endpoint. A 2-sided p value <0.05 was considered statistically significant.

RESULTS

The study population consisted of 156 consecutive patients treated between July 2012 and July 2014 at 2 centers with second-generation DCB for native coronary artery disease (87 with Restore and 69 with Elutax SV), that were prospectively entered in the database. Thirty-five percent of patients had diabetes, and clinical indication was stable angina in 82, unstable angina in 31, and non-ST-segment elevation myocardial infarction in 43 patients. Procedural success was achieved in all patients.

TABLE 2 Procedural Characteristics

	All DCB Population, Native Vessels (N = 156)	No Dissection Cohort (n = 104)	Dissection Cohort (n = 52)	p Value
Radial approach	144 (92.3)	96 (92.3)	48 (92.3)	0.95
Total occlusion	18 (11.5)	9 (8.7)	9 (17.3)	0.47
Reference vessel diameter, mm	2.83 (2.12–3.01)	2.87 (2.15–3.0)	2.80 (2.07–2.97)	0.21
Minimal lumen diameter, mm	0.4 (0.0–0.73)	0.37 (0.03–0.65)	0.41 (0.00–0.79)	0.11
Stenosis severity, %	83 (72–100)	82 (71–100)	84 (70–100)	0.18
Lesion length, mm	21 (10–33)	19 (10–28)	22 (12–33)	0.10
Severe-moderate calcification (visual estimation)	100 (64.1)	60 (57.7)	40 (76.9)	**0.01**
Pre-dilation balloon diameter, mm	2.45 (2.0–3.0)	2.35 (2.0–3.0)	2.5 (2.0–3.0)	**0.04**
DCB diameter, mm	2.55 (2.0–3.0)	2.50 (2.0–3.0)	2.60 (2.0–3.0)	**0.035**
DCB length, mm	25 (15–30)	24 (15–30)	25 (15–30)	0.37
Max pressure during DCB angioplasty, atm	12 (8–14)	11 (9–14)	12 (8–15)	0.49
DCB inflation duration, s	35 (30–45)	37 (32–45)	34 (30–42)	0.33
OCT/IVUS guidance	15 (9.6)	11 (10.6)	4 (7.7)	0.13
Minimal lumen diameter after PCI, mm	2.21 (1.75–2.67)	2.17 (1.75–2.58)	2.24 (1.84–2.67)	0.22
Procedural success	156 (100)	104 (100)	52 (100)	0.87
Periprocedural myocardial infarction	21 (13.5)	13 (12.5)	8 (15.4)	0.42
Bivalirudin	15 (9.6)	9 (8.7)	6 (11.5)	0.23
Dual antiplatelet therapy				
ASA + clopidogrel	130 (83.3)	85 (81.7)	45 (86.5)	0.24
ASA + ticagrelor/prasugrel	26 (16.7)	19 (18.3)	7 (13.5)	0.36

Values are n (%) or median (interquartile range). Values in **bold** have reached statistical significance.

ASA = acetylsalicylic acid; DCB = drug-coated balloon; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PCI = percutaneous coronary intervention.

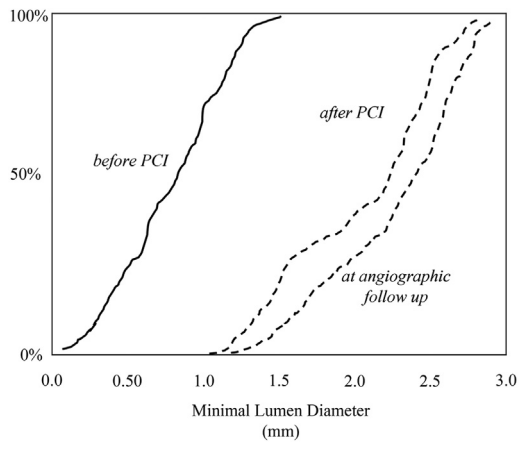
TABLE 3 Angiographic Follow-Up of Patients With Dissection After DCB PCI

	Dissection Cohort (n = 48)
Reference vessel diameter, mm	2.87 (2.11 to 2.98)
Minimal lumen diameter, mm	2.42 (2.22 to 2.66)
Diameter stenosis, %	12 (8 to 20)
LLL, mm	0.14 (−0.14 to 0.42)
Complete vessel healing	45 (93.8)
Binary restenosis	3 (6.2)

Values are median (interquartile range) or n (%). Follow-up was at 201 days (interquartile range 161 to 250 days).

LLL = late lumen loss; other abbreviations as in Table 2.

FIGURE 1 MLD Before DCB PCI, After DCB PCI, and at Angiographic Follow-Up in Patients Left With a Dissection



Notably, there was a diffuse lumen enlargement at angiographic control. DCB = drug-coated balloon; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention.

For the purpose of this analysis, we studied the 52 patients that had an angiographically detectable dissection after DCB angioplasty. All patients of this cohort underwent programmed coronary angiography after 6 to 9 months. Baseline clinical characteristics and clinical indication to PCI of the entire population and of the 2 cohorts are shown in Table 1. The dissection study group did not differ significantly from the entire DCB group, if we exclude a higher incidence of left anterior descending artery as the culprit vessel, the degree of calcification of the culprit lesion, the size of balloon used for predilation, and the size of the DCB (Table 2). Baseline angiographic characteristics are shown in Table 2. Of note, the vessel diameter was 2.83 mm in the entire population, and 2.80 mm in the dissection population.

Of the 52 patients with residual dissection after DCB PCI, 4 had a prosthesis implanted (2 a bare-metal stent, 1 a DES, and 1 a biovascular scaffold). The reason for implanting a stent/scaffold was impairment of distal flow in 3 patients, and the presence of a spiral, type D dissection in 1.

All patients with a final dissection underwent scheduled angiographic follow-up with quantitative coronary assessment, that was undertaken after 201 days (interquartile range 161 to 250 days). Angiographic outcome is presented in Table 3. Of note, LLL was as low as 0.14 ± 0.28 mm in this group. We also observed a late lumen enlargement in the treated segments (Figure 1).

Complete vessel healing at angiography was observed in 45 of 48 patients (93.8%) (Figure 2). The 3 patients that had an unhealed dissection had, respectively, a type A, type B, and type C coronary dissection after the index PCI. TLR occurred in 3 patients (6.2%) in the dissection cohort and in 8 patients (5.3%) in the entire DCB population (p = 0.49) (Figure 3). Of the 3 patients that underwent TLR in the dissection cohort, the first 2 had recurrence of angina after 4 and 6 months, respectively; angiography showed subocclusive coronary stenoses (of 85% and 90%, respectively) at the site of the previous PCI that were successfully treated with DES implantation. The third patient was asymptomatic but had a persisting, chronic coronary dissection discovered at angiographic follow-up that was sealed with DES implantation.

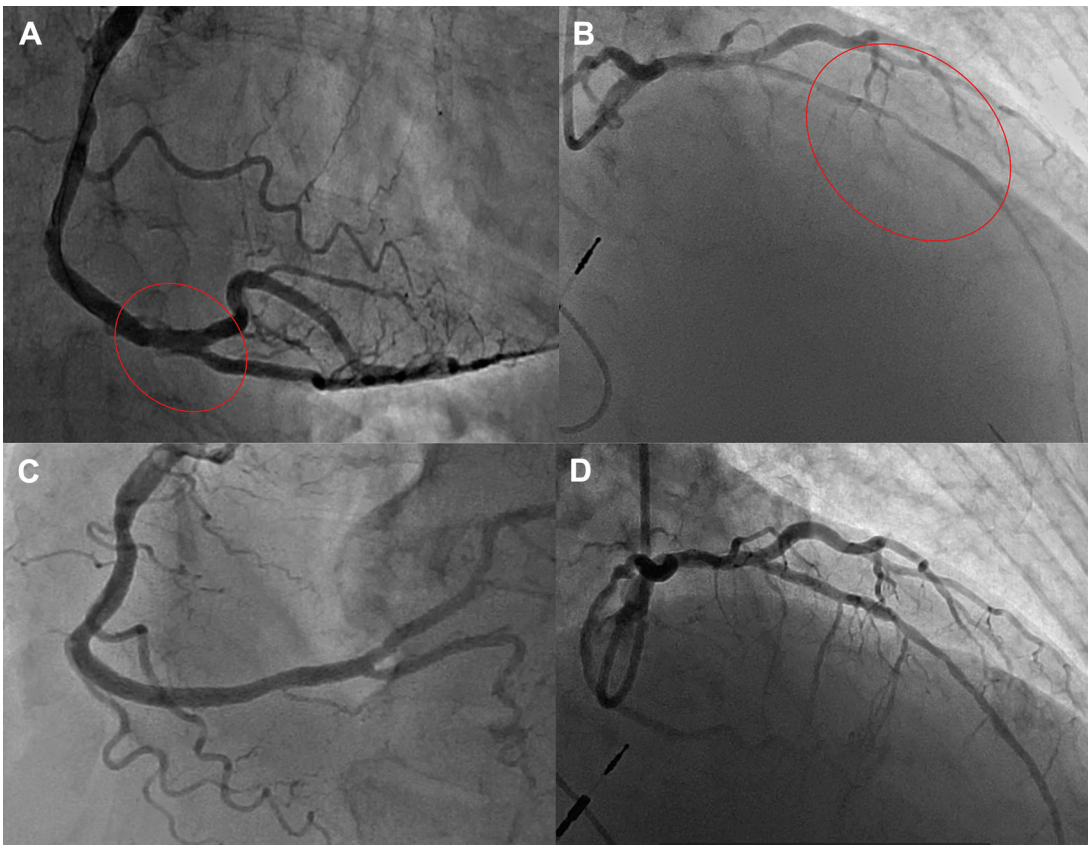
The other clinical endpoints showed no significant differences between the whole group and the groups with and without dissection (Figure 3). Interestingly, we did not observe cases of target vessel myocardial infarction during the entire clinical follow-up (average length 9 ± 3 months). Finally, there were no significant differences between the 2 devices tested in terms of clinical and angiographic endpoints.

DISCUSSION

This prospective observational study describes the first consecutive series of patients treated with DCB for native coronary artery disease and with final dissection left “unsealed” with prosthesis. Our results confirm that leaving a non-flow-limiting dissection untreated after DCB PCI is safe and not associated with an increase in myocardial infarction and TLR, despite the short-term (1 month) dual antiplatelet treatment. Notably, we did not observe a correlation between the type of dissection at baseline (type A, B, or C) and the propensity to healing (Figure 4).

DCB were developed to overcome neointimal hyperplasia and have been first tested in the in-stent restenosis setting with good results maintained for years (3,9). However, the use of DCB for the treatment of native vessels seems particularly encouraging, especially in the case of small vessels and distal lesions, where the encumbrance of a stent may limit its potential and is associated with increased rates of restenosis and stent thrombosis. However, the application of this technology as standalone procedure in de novo lesions has resulted in conflicting results. After some early mistakes, such as the ones depicted in the PICCOLETO (Paclitaxel-Eluting Balloon Versus Paclitaxel-Eluting Stent in Small

FIGURE 2 **Angiographic Outcome of Dissections Left After DCB Angioplasty**



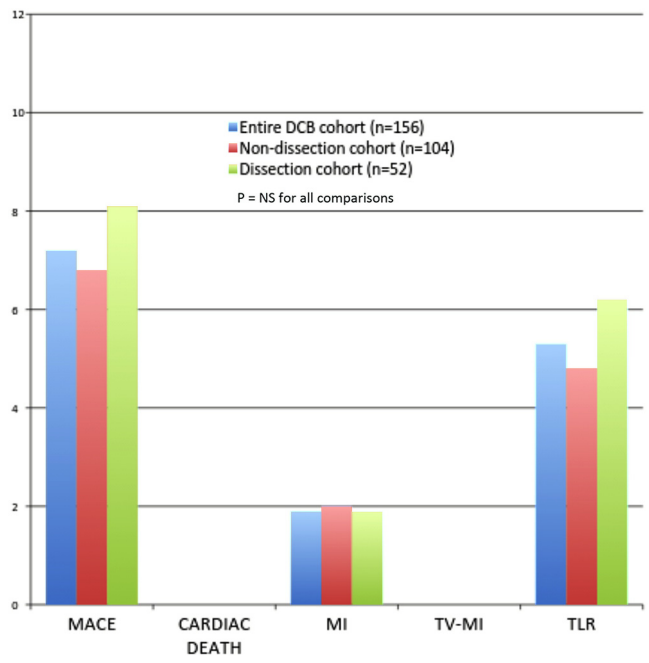
A and B show the final dissections (respectively, a type C and a long type A dissection, **red circles**); after 6 months, both dissections were healed **(C and D)**. DCB = drug-coated balloon.

Coronary Artery Diseases) study (10,11), a newer generation of DCB has been tested in the BELLO (Balloon Elution and Late Loss Optimization) study for the treatment of native coronary vessels. Here, DCB overcame Taxus DES for the treatment of small vessel disease in terms of the primary endpoint of LLL (0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; 95% confidence interval: −0.34 to −0.09; p = 0.001) (12). Recently, the 2-year follow up of the BELLO study, that showed persisting good results of DCB in terms of clinical endpoints, has been published. (13) Similar encouraging results for this technology in native coronary vessels were shown in large registries with different, new-generation DCB (14,15).

This study was performed with 2 devices of the latest available technology, that provides optimal paclitaxel delivery to the vessel wall and contemporarily allows its longer persistence.

The central point of our findings is the safety of leaving a dissection after DCB angioplasty. Early experiences have shown how leaving a dissection after plain old balloon angioplasty was associated with increased rates of thrombotic events, early reocclusion, and recurrence of restenosis, and this was one of the main indications for the use of stents in an earlier era (16). The widespread use of more potent antiplatelet regimens (e.g., the association of aspirin with a $P2Y_{12}$ receptor inhibitor) has undoubtedly improved the early outcome of this type of patient. In the early stent era, a previous series of patients treated consecutively with plain angioplasty and with a final dissection, despite a very low occurrence of thrombotic events and an acceptable rate of restenosis (12%), 36.7% of dissections left were still visible at 6-month angiographic follow-up (17). With this current study, we have opened the hypothesis that the effect of paclitaxel, when correctly delivered to the vessel wall, may have a role in facilitating the healing of coronary vessels.

FIGURE 3 Clinical Follow-Up After 9 Months in the Entire Population and in the Dissection and No-Dissection Cohorts



p Values are not significant for all comparisons. DCB = drug-coated balloon; MACE = major cardiovascular event(s); MI = myocardial infarction; TLR = target lesion revascularization; TV = target vessel.

FIGURE 4 The Fate of Dissections After DCB Angioplasty

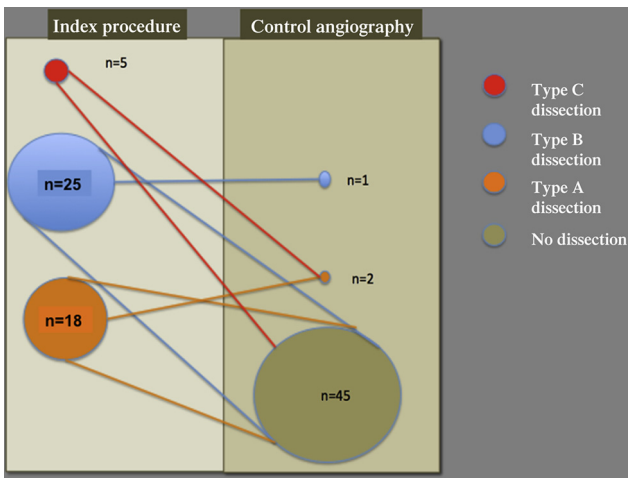


Figure shows what happened to dissections at 6-month angiography: 45 were healed and 3 were chronic. There was not an apparent correlation between the type of initial dissection left after DCB angioplasty and its fate. We followed the NHLBI classification for coronary dissections. DCB = drug-coated balloon; NHLBI = National Heart, Lung, and Blood Institute.

This effect was already described in a post-hoc analysis of the THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) study (6), where patients with femoropopliteal disease were randomized to simple angioplasty or DCB. In this analysis, patients treated with DCB resulting in final dissection of any grade had significantly lower LLL than patients with dissection after simple angioplasty (0.4 vs. 1.9 mm; $p = 0.001$), especially if the dissection grade was severe (type C to E) (0.4 vs 2.4 mm; $p = 0.05$). This result was maintained for all the duration of the 2-year follow-up, with a TLR of 10% versus 56% respectively ($p = 0.002$) (6). In another study, Agostoni et al. (18) have found how leaving small dissections after DCB angioplasty for in-stent restenosis resulted in complete dissection healing at optical coherence tomography after 6 months. In addition to this information, we also found that our patients, who did not have a "caged" coronary artery because they did not have in-stent restenosis, also had an improved late lumen gain, as already described in another series of patients treated with DCB for native coronary vessel disease (19). This late lumen enlargement (**Figure 1**) is another interesting effect of DCB that needs further, dedicated analysis.

In this study, we decided to limit the degree of dissections left to a low-medium grade (type A to C) because of ethical reasons (the eventual vessel occlusion would result in myocardial infarction). Now with our results, if the dissection is of low-medium grade, it seems safe to leave it untreated. In fact, data from the literature show how any stent strategy associated with DCB use is unsafe or yields unsatisfactory results (20,21). There are some initial data on the use of DES after DCB, but such data are limited in number and are without angiographic follow-up (22), thus the contemporary use of 2 different antirestenotic drugs with stent metal layers needs to be better understood before recommending this strategy. Moreover, in this case, the advantages of using a DCB are immediately lost (23).

STUDY LIMITATIONS. First, the population is limited and derives from 2 centers expert in this type of PCI, thus it may not be reproducible everywhere without an adequate learning curve. Moreover, we have to disclose an initial bias at the time of decision of leaving the dissection untreated. So far, these results are not easily reproducible in all settings. Our findings, although a confirmation of other previous studies, are the first assessment of this property of new-generation DCB in native coronary lesions, and need to be validated in other ad hoc clinical studies.

CONCLUSIONS

In a consecutive series of patients treated with new-generation DCB for native coronary artery disease and with a final non-flow-limiting dissection, these lesions tended to heal despite their initial severity. After DCB angioplasty, a strategy of bailout stenting should be reserved to more severe, flow-limiting dissections.

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PERSPECTIVES

WHAT IS KNOWN? DCB are a useful tool for the treatment of small coronary arteries. However, little is known regarding the fate of dissections left unsealed after DCB PCI.

WHAT IS NEW? With this study, for the first time in the coronary tree, we showed a pro-healing effect of DCB when a final dissection was left at the end of PCI.

WHAT IS NEXT? We now need an adequately powered study (e.g., a randomized controlled study) to test this preliminary report in a broader population of coronary artery disease patients.

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KEY WORDS angiographic follow-up, coronary dissection, dissection healing, drug-coated balloon

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Letter to the Editor

Drug-coated balloon angioplasty: An intriguing alternative for the treatment of coronary chronic total occlusions

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Dear Editor,

The treatment of coronary chronic total occlusions (CTOs) is one of the most exciting and, at the same time, delicate challenges for the interventional cardiologist. In the last few years specific devices have been implemented in order to increase the rate for a successful CTO recanalization. Current treatment options are drug-eluting stents, surgery or medical treatment. We here present an emblematic case of a new approach to this disorder.

An 80-year-old male was admitted at our department for worsening effort angina. In his medical history he had an anterior myocardial infarction managed with PCI and DES implantation of the left anterior descending artery (2008), and thereafter he underwent successful simple angioplasty of the ostium of 2nd obtuse marginal (OM2) due to subocclusive stenosis (Fig. 1A–B, Movie 1). Subsequently he developed a HCV-related hepatitis with episodes of gut and upper airway bleeding.

Coronary angiography showed a chronic total occlusion (CTO) of the ostial OM2 (Fig. 1C, Movie 2) for which we attempted antegrade recanalization. The lesion was not easily wired by a 12-g CTO guidewire supported by a 1.5 mm balloon. We thus performed further predilatations with 2.0 and 2.5 mm balloons obtaining adequate angiographic result. Given the high bleeding risk of the patient, we delivered a 2.5/30 mm drug-coated balloon (DCB), obtaining a good angiographic result with TIMI 3 grade flow and without visible dissection (Fig. 1D, Movie 3). The patient was discharged on dual antiplatelet treatment (DAPT) and after 30 days withdrew clopidogrel. Six-month scheduled coronarography showed persisting good angiographic result with improved lumen gain (Fig. 2A–B, Movie 4). One year later, the patient was still angina-free and had no ischemic or bleeding adverse events.

The use of DCB for the management of coronary artery disease is increasing for several clinical indications/anatomical settings. Specifically, we believe that this device could represent a new intriguing alternative to stents for the treatment of CTO as well [1]. To the best of our knowledge, this is a unique case in which a coronary CTO was managed with a DCB-only strategy. DCB delivers paclitaxel with a single shot and determines a homogeneous distribution of the drug on the vessel wall, resulting in a high concentration during the first days, when the restenotic process is developing [2]. Another advantage is that no permanent prosthesis is delivered, thus reducing the risk of late thrombotic events and the need for prolonged DAPT [3]. More so, the increased risk of late thrombotic events of newer generation DES may be explained by a delayed struts coverage if delivered for a CTO instead of other coronary lesions, thus requiring longer DAPT [4]. Conversely, a DCB-only strategy allows DAPT withdrawal after 2–4 weeks only, especially in patients at higher bleeding risk [5].

We believe that DCB may be a reasonable alternative to stents for the management of CTO. A dedicated study of DCB-only angioplasty seems a provocative idea and is eagerly awaited, especially for those patients that cannot undergo prolonged DAPT.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.03.223.

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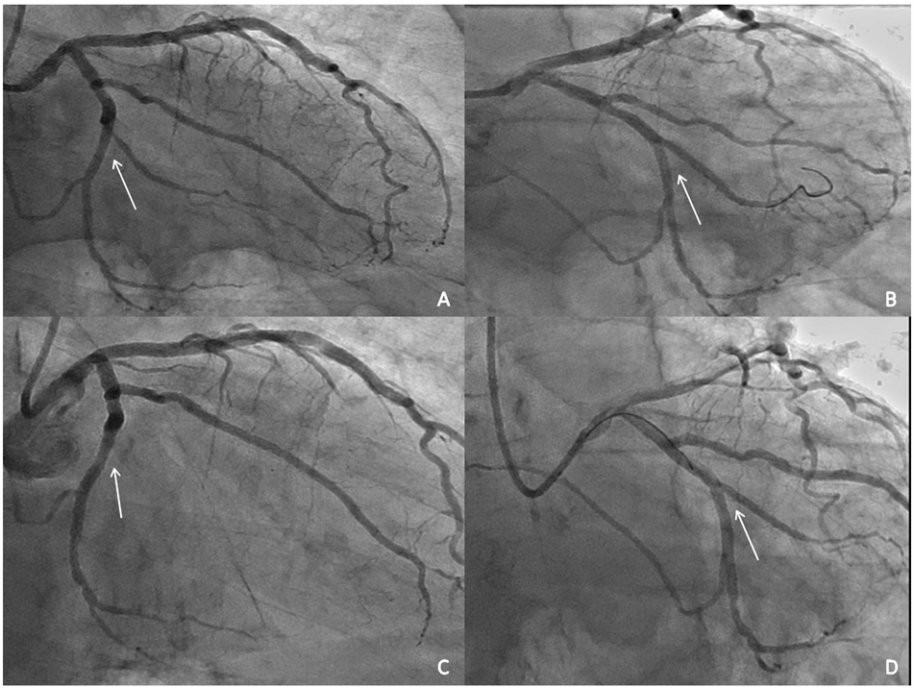

Fig. 1. A: subocclusive stenosis of the ostium of 2nd obtuse marginal branch (OM2). 1B and Movie 1: final angiographic result after simple balloon angioplasty. 1C and Movie 2: chronic total occlusion of the ostium of OM2. 1D and Movie 3: final angiographic result after drug-coated balloon angioplasty.

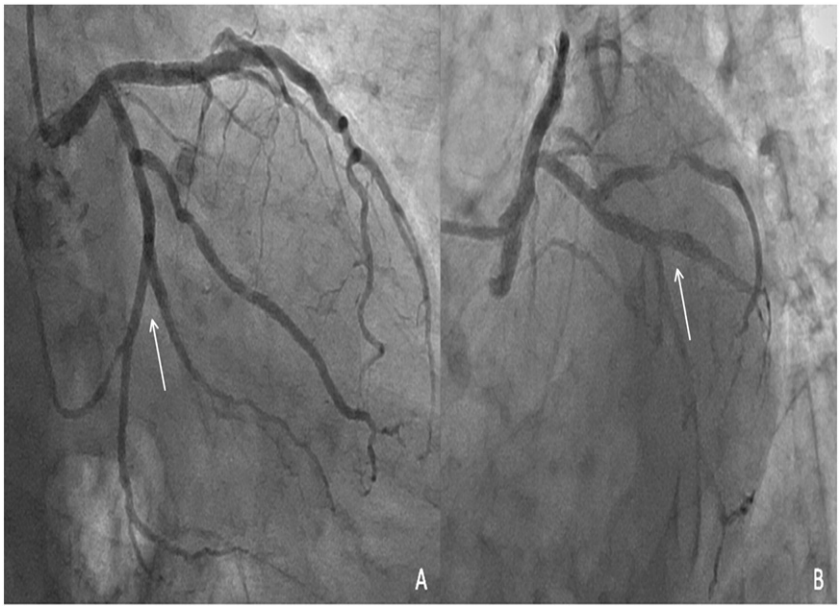

Fig. 2. A–B and Movie 4: six-month angiographic follow-up showing good patency of index lesion and increased vessel diameter.

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First experience of drug-coated balloons for treatment of bioresorbable vascular scaffold restenosis☆

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ABSTRACT

Objectives: The aim of this study is to evaluate the role of drug-coated balloons (DCB) for the management of bioresorbable vascular scaffold (BVS) restenosis.
Methods and results: In a series of 25 BVS restenosis discovered during systematic angiographic follow up of 246 consecutive BVS implantations at our institution, DCB was used as a primary therapeutic tool in 9 patients and 3 different types of DCB were used. Follow-up coronary angiography at 12 months after DCB treatment was performed to all the patients. Among the 9 patients treated with DCB, angiographic follow up revealed failure in two patients that experienced type III restenosis (both of them treated with the same type of DCB). Both patients were treated with drug eluting stent implantation.
Conclusions: In this case series of consecutive patients with BVS restenosis, the use of certain types of DCB is safe and effective in order to maintain vessel patency at mid-term follow up. Despite the small sample size and the study limitations, DCB can provide therefore an alternative treatment option in this setting, avoiding the implantation of further metallic stents in a patient where a different strategy was initially planned.

1. Introduction

The use of drug-coated balloons (DCB) is one of the treatments of choice for both bare metal stent and drug-eluting stent (DES) restenosis [1]. Bioresorbable vascular scaffolds (BVS) are one of the most recent revolutionary steps in interventional cardiology. Studies are ongoing to evaluate the long-term efficacy of these biodegradable devices in a real world setting. There are limited data regarding the clinical outcome following target lesion revascularization (TLR) for BVS failure, with the optimal management currently unclear [2]. Several treatments are commonly used in this setting, including DES, re-BVS and DCB use. Currently, only few data are addressing the safety and the efficacy of DCB in the management of BVS restenosis.

The aim of this study, in the form of case series of consecutive patients, is indeed to evaluate the role of DCB in the management of BVS restenosis.

2. Methods

Out of 246 consecutive BVS implantations (Abbott Vascular, Santa Clara, CA, USA) between January 2013 and December 2015 performed at our institution, 210 underwent scheduled angiographic follow up after institutional review board approval and patient's informed consent. At a mean of 12 months, coronary angiography revealed 26 in-scaffold restenosis, defined as >50% restenosis at treatment site: 4 of them were left untreated due to the absence of evident signs of myocardial ischemia, 9 underwent DES implantation, 3 underwent further BVS implantation due to edge-restenosis, 1 underwent coronary artery bypass grafting and 9 patients received revascularization with DCB. At 12 months, a second coronary angiography was scheduled for the patients treated with DCB. Quantitative coronary angiography (QCA) performed by one single expert operator was used for the assessment of all procedures. Optical coherence tomography (OCT) (Ilumien, St. Jude Medical, MN, USA) was used for the assessment of the scaffold failure. Angiographic pattern of scaffold restenosis was classified according to Mehran's classification [3]. Data are presented as mean ± SD. Categorical variables are expressed as count and percentages.

3. Results

From the analysis of our data emerges a complex population. Table 1 describes the clinical characteristics of the patient and baseline procedural data, whereas Table 2 describes the procedural characteristics of

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Table 1
Clinical characteristics and procedural details at the initial procedure (time of BVS implantation).

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Clinical characteristics	Age	56	42	57	70	55	76	81	58	79
	Sex	Female	Male	Male	Male	Male	Male	Male	Male	Male
	DM	No	No	Yes	No	Yes	No	No	Yes	No
Initial Procedure	Vessel	LCX-OM1	D2	Distal LAD	Prox. RCA	Proximal LCX	RI	Distal. RCA	LCX-OM1	Prox. LAD
(BVS implantation)	Lesion length (mm)	25	18	25	25	15	25	25	24	15
	RVD (mm)	2.75	2.5	2.5	3.5	2.5	2.5	3	2.5	3
	MLD (mm)	0.75	0.1	0.75	0.4	0.5	0.3	0.1	0	0.3
	% Stenosis	70	99	70	90	80	90	99	100	90
	Lesion type	B1	B1	B1	B1	B1	Type II ISR	Type II ISR	C	B1
	Degree of calcification	No	No	Mild	No	Mild	No	No	Mild	No
	Pre-dilatation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Scaffold length (mm)	28	18	28	28	18	28	28	28	18
	Scaffold diameter (mm) Mean= 2.66 ± 0.35 mm	2.5	2.5	2.5	3.5	2.5	2.5	2.5	2.5	3
	Post-dilatation	yes	yes	yes	yes	yes	yes	yes	yes	yes
	MLD	2.5	2.5	2.5	3.5	2	2.5	3	2.5	3
	Residual stenosis post-procedure(%)	0	0	0	0	20	0	0	0	0
	Acute again (mm)	2	2.4	1.75	3.1	16	2.2	2.9	2.5	2.7

the DCB procedure. At baseline, 6 patients had type B1 lesions, 1 type C lesion and 2 had type II ISR. Mean BVS diameter was 2.7 ± 0.35 mm and mean scaffold length was 24.7 ± 5 mm. The average time from the index procedure to scaffold failure was 12 ± 3 months. At index procedure, all the lesions were predilated by semi-compliant balloons in order to reach a <30% lesion stenosis. The mean diameter of the DCB was 2.6 ± 0.33 mm while the mean DCB length was 24.3 ± 7.8 mm (Table 2) and 3 different types of DCB were used.

Angiographic follow-up after the use of DCB was available for all the patients at a mean of 12 ± 2.6 months (Table 3). We observed two cases of DCB failure, both of them treated with Restore DCB (Cardionovum, Germany). For demonstrative purposes, 3 lesions were represented in Figs. 1–3. In particular, the first lesion was treated by 2.5 × 28 mm BVS at the LCX–OM1 bifurcation. The patient had unstable angina and coronary angiography revealed BVS failure with an 80% stenosis. This lesion was managed as mentioned by the use of 2.5 × 25 mm Restore DCB. At the scheduled angiographic follow-up we observed a recurrent 80% type III ISR, which was treated by the implantation of DES.

The other case of DCB failure the patient had received a 2.5 × 18 BVS in the proximal LCX. After 14 months angiographic follow-up performed for myocardial ischemia at stress test showed BVS failure with a 99% stenosis, and was managed by the use of one 2.5 × 20 Restore DCB. At the 6 months scheduled angiographic follow-up, the patient had type III restenosis that was managed by the implantation of 1 DES (Fig. 1).

During angiographic follow up, late lumen loss observed with DCB was 0.68 ± 0.7 mm. Clinical follow up revealed no hard clinical events.

4. Discussion

The BVS, heralded as the "fourth revolution in interventional cardiology [4], offers the possibility of transient scaffolding of the vessel to prevent acute vessel closure and recoil while eluting an antiproliferative drug to counteract the constrictive remodeling and the neointimal hyperplasia.

Absorb-BVS is the first drug-eluting BVS available for human use and is composed of PLLA and PDLLA. The bioresorbable polymer poly (L-lactide) (PLLA) scaffold is coated with a blend of the antiproliferative drug everolimus and bioresorbable polymer poly (D, L-lactide) (PDLLA) and pre-mounted on a rapid exchange (RX) scaffold delivery system. The scaffold is comprised of a series of circumferentially oriented sinusoidal rings that open during expansion. Two platinum markers are embedded at each end to enable fluoroscopic visualization, as the scaffold material is not radiopaque [5]. The first-generation of BVS was tested in the ABSORB Cohort A study, which showed late lumen enlargement, feasibility of non-invasive imaging with computed tomography (CT) scanning, and restoration of vasomotor and endothelial function at 2 years [6]. The second-generation of the device, tested in the ABSORB Cohort B, demonstrated a MACE rate of 9.0% (3 non-Q-wave MI, 6 ischemia-driven TLR, and no cardiac death) during the 2-year follow-up, with no alarming safety issues [7].

Later, Absorb II trial aimed at assessing the efficacy and safety of BVS in a broader patient population, and BVS was directly compared to Xience DES (Abbott Vascular, USA) [8]. The 3-year follow up of the trial, recently published, revealed a higher rate of target lesion failure

Table 2
Procedural details of the index procedure (Time of DCB use).

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Procedural Characteristics of the index procedure (DCB use)	Time from BVS implantation Mean= 12 ± 3 months	17	7	11	11	14	11	12	13	11
	MLD	0.5	0	0.75	1	0.3	0.75	1.09	0	0.9
	% stenosis	80	100	70	70	99	70	60	100	70
	DCB type	Restore	Elutax SV	Elutax SV	In.Pact Falcon	Restore	In.Pact Falcon	In.Pact Falcon	Elutax SV	Elutax SV
	DCB length Mean= 24.3 ± 7.8 mm	25	30	20	20	20	14	20	40	30
	DCB diameter Mean= 2.61 ± 0.33 mm	2.5	2	2.5	3	2.5	2.5	3	2.5	3
	Final MLD	2.5	2	2.5	3	2	2.5	3	2.5	3
	Final % stenosis	0	0	0	0	20	0	0	0	0

Table 3
Angiographic and clinical follow up after DCB use.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Follow up after DCB	Time from DCB PCI (months)	7	8	8	12	6	6	15	6	11
	MLD (mm)	0.5	2	2.5	3.5	0.5	1.75	1.8	1.5	2.7
	% Stenosis	80	0	0	0	80	30	28	40	10
	Late lumen loss Mean= 0.68 ± 0.7 mm	2.25	0	0	0	2	0.75	1.2	1	0.3
	Death	No	No	No	No	No	No	No	No	No
	MI	No	No	No	No	No	No	No	No	No
	TLR	Yes	No	No	No	Yes	No	No	No	No

in the BVS group (7 vs. 3%, p = 0.07). In this trial, BVS failure was either caused by scaffold thrombosis (including 6 very late definite cases) and restenosis (11 cases at 3 years).

In terms of restenosis, many mechanisms were suggested to explain BVS failure, such as: neointimal hyperplasia, neoatherosclerosis, BVS collapse, fracture, edge phenomenon and late dismantling. In our experience, BVS failure is most likely caused by neointimal proliferation if it occurs during the first months. After the device has lost its integrity (usually after 6–12 months), contrary to metallic stents BVS failure can be also caused by scaffold recoil, although limited data are available in the literature on this topic [9]. Based on the assumption that BVS and metallic stents both share the same pathogenesis for restenosis, accordingly DCB appears to be an appealing option in this subset of patients. In our study, immediate and late angiographic success was achieved in 7 patients, all treated with latest-generation DCB. We can only speculate on the pathogenesis of BVS failure in this case series; however, the use of intravascular imaging seems to us an important tool in order to understand its etiology.

Historically, failure of re-PCI after ISR occurs in 30–70% of the cases regardless of the technique used [10,11]. In our study, DCB failure occurred in 2 patients who were both treated with Restore DCB. Nowadays, it is quite clear how all DCB were not created equal, probably because of the complex mechanisms under this technology that firstly aim at protecting paclitaxel while reaching the target lesion, and later should allow its diffusion and persistence in the vessel wall [11,12].

This case series has several limitations that need to be accounted. First, despite the complete angiographic follow up, sample size is small. Second, although clinical and angiographic outcomes are promising, the nature of this case series does not allow a comparison of different types of DCB. Larger studies, prospectively designed, with a larger population and a comparison with DES seem the best way to deeply understand if DCB may have a role for the treatment of BVS restenosis.

5. Conclusions

Management of BVS restenosis requires a deep understanding of its pathogenesis. In this case series of consecutive patients treated with DCB we suggest that this strategy is a safe and effective option to maintain the vessel patency at mid-term. Larger studies to address the etiology of BVS failure and to assess the role of DCB in such lesions are needed.

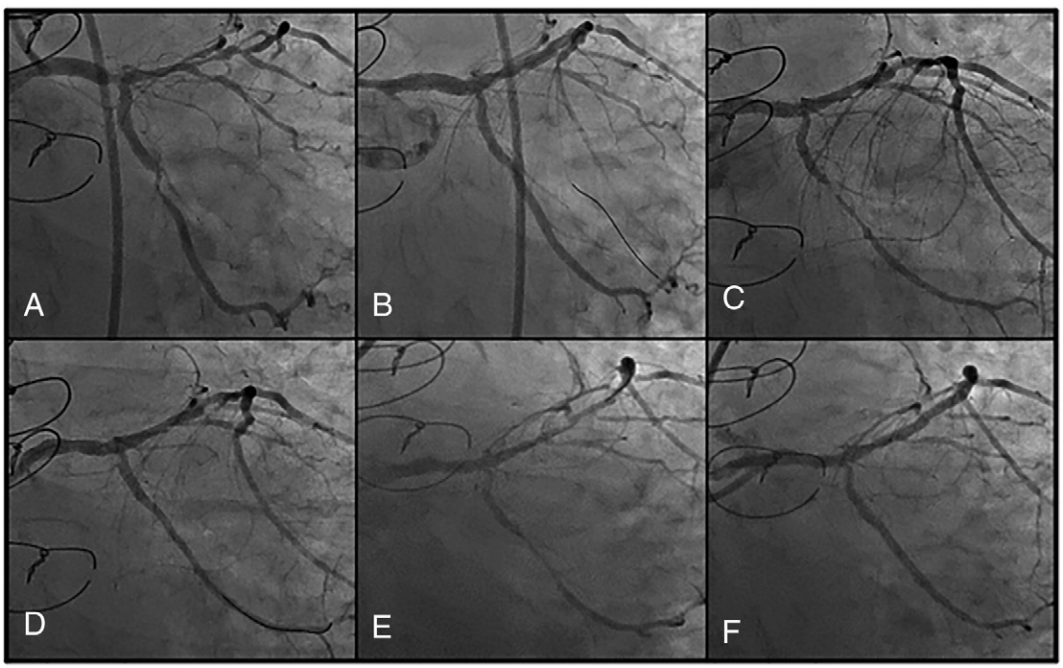

Fig. 1. A: significant stenosis at mid LCX at the initial procedure, B: result after BVS implantation. C: BVS restenosis, D: immediate angiographic result after DCB use, E: OCT revealing well apposition of the BVS, F: angiographic follow up showing DCB failure, F: OCT showing scaffold failure secondary to neointimal hyperplasia, G: angiographic result after DES implantation (Patient 1).

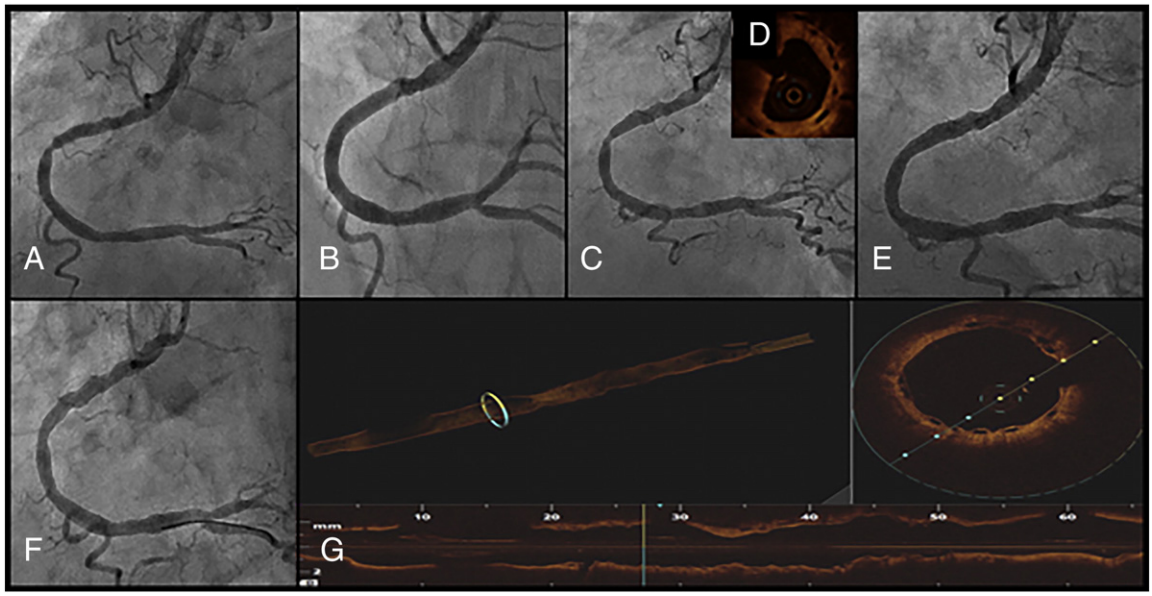

Fig. 2. A: significant stenosis at mid RCA during the initial procedure, B: angiographic result after BVS implantation, C: BVS restenosis occurred at 11 months, D: OCT analysis, showing neointimal hyperplasia within the BVS with preserved integrity of the scaffold, E: angiographic result immediately after DCB, F: angiographic follow up after 12 months, G: OCT run showing sustained good result at 12-months angiographic follow-up after DCB use (Patient 4).

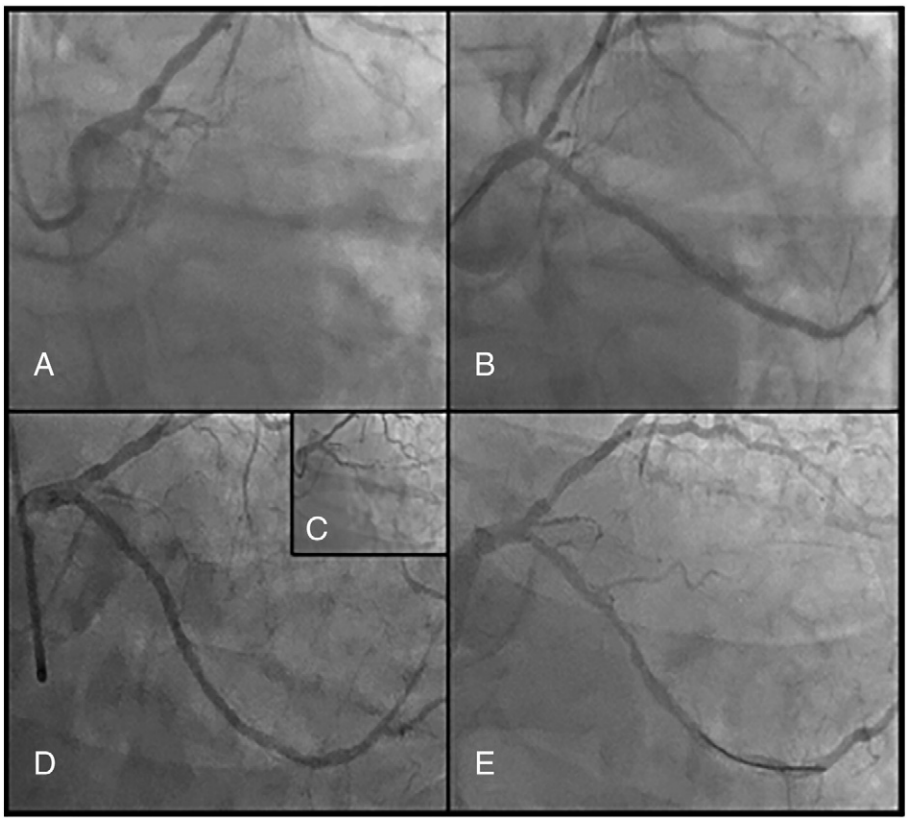

Fig. 3. A: total occlusion at the proximal LCX, B: angiographic result after BVS implantation, C: BVS restenosis occurred at 13 months, D: angiographic result after DCB use, E: angiographic follow up showing mild restenosis (Patient 8).

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PICCOLETO II: More Support for DCB Safety and Efficacy in Small Coronaries

In-lesion late lumen loss was similar for a gel-based balloon versus an EES, but a trend was seen for more thrombosis with the stents.

By L.A. McKeown October 04, 2019

SAN FRANCISCO, CA—A new gel-based paclitaxel drug-coated balloon (DCB) outperformed an everolimus-eluting stent (EES) in terms of late lumen loss and resulted in comparable diameter stenosis, binary restenosis, and short-term clinical outcome in patients with small-vessel CAD, results from PICCOLETO II suggest.

Presenting here at TCT 2019, Bernardo Cortese, MD (Clinica San Carlo, Milan, Italy), said that although the study is small and not powered for hard endpoints, it adds to existing data hinting that drug delivery via a balloon may optimize outcomes better in small vessels than a stent.

"The best-in-class drug-eluting stents show a rate of target lesion failure

the superiority of DCB in terms of angiographic outcome," he told TCTMD.

PICCOLETO II is the latest trial to show DCB as a potential alternative to DES in patients with small-diameter lesions. At EuroPCR 2019, investigators from the BASKET-SMALL 2 trial presented new angiographic data showing similar late lumen loss with both treatments out to 1 year. Surprisingly, the angiographic data also showed eight cases of stent thrombosis in the DES group versus no complete thrombotic vessel occlusions in the DCB group. The PICCOLETO II data line up with those results.

"Similarly, we found a 1.8% rate of stent thrombosis in the EES arm, and no thrombosis in the DCB arm," Cortese told TCTMD. "We thus confirm the findings of BASKET-SMALL 2. The opportunity not to leave a stent in small vessels may protect from thrombotic events."

Gel May Improve Drug Delivery

PICCOLETO II is a follow up to the PICCOLETO study, in which patients with stable or unstable angina undergoing PCI of small coronary vessels (≤ 2.75 mm) were randomized to the Dior DCB (Eurocor) or Taxus DES (Boston Scientific).

As Cortese explained to TCTMD, the first study used a balloon that had paclitaxel sprayed onto the surface. The drug was lost during transit and manipulation, which the researchers believed prevented it from having the desired effect. For PICCOLETO II, they instead used the Elutax SV (Aachen Resonance), "a new-generation DCB with a gel which protects and mostly helps [paclitaxel] to be delivered to the vessel wall, and persist there for 4 to 6 weeks in order to obtain its effect," Cortese noted. The gel is hydrophilic, which is intended to help the drug stay on the balloon longer and prolong the absorption time. The paclitaxel dose on the balloon is 2.2 µg/мм^2 .

For the multicenter, open-label trial, 118 patients similar to those in the earlier PICCOLETO trial were randomized to the DCB and 114 to the Xience EES (Abbott Vascular). Predilatation was strongly recommended for both strategies, with at least a 30- to 60-second dilatation of the balloon but no specific advice for the EES.

Aside from a higher percentage of renal failure patients in the EES group, there were no significant baseline differences between the two arms. More than half of patients in each group had stable angina and about 20%

Predilatation was performed in 69% of the EES group and 84% of the DCB group, while postdilatation was performed in nearly 60% of the EES group and only 3% of the DCB group ($P = 0.001$). The number of devices used in the DCB group was lower than in the EES arm, but length of devices was a bit longer (8.2 mm vs 6.9 mm; $P = 0.04$).

At 6 months, in-lesion late lumen loss, the primary endpoint, was 0.17 ± 0.39 mm in the EES group and 0.04 ± 0.28 mm in the DCB group, meeting noninferiority criteria for the balloon ($P = 0.03$). There were no significant differences in clinical outcomes, although a trend was seen toward higher TLR in the DCB group ($P = 0.23$).

Minimum lumen diameter, a secondary endpoint, increased more in the DES group (from 0.83 mm before the procedure to 2.29 mm after the procedure) than in the DCB group (0.82 mm to 1.89 mm). Percent diameter stenosis changes, however, were similar in both arms. Other secondary endpoints of percent diameter stenosis and binary restenosis were similar between the treatment arms at 6 months (both in-stent and in-segment).

Smaller Lesions, Bigger Payoff With DCBs?

According to Cortese, the PICCOLETO II outcomes with regard to late lumen loss are among the best so far in small-vessel disease, a setting that includes studies such as PEPCAD SVD, BELLO, RESTORE SVD, and FASICO NATIVES.

Discussant Fernando Alfonso, MD, PhD (Hospital Universitario La Princesa. Madrid, Spain), said he was “nicely surprised” by the results of PICCOLETO II.

In theory, as you go smaller and smaller, the benefits of non-scaffold-based therapy might be even greater," added discussant Robert M. Bersin, MD (Swedish Heart & Vascular, Kirkland, WA). “Have you broken this down to the very small [lesion] subsets, like 2.22 mm and smaller to see whether or not you get a signal of superiority with DCB? Overall you have equivalence here, but you may even be superior the smaller you go.”

Cortese responded that the study is a proof-of-concept, and while that possibility does exist, it remains to be shown in future trials.

Given that the drug on the balloon is paclitaxel and that a meta-analysis recently turned the endovascular community on its head with suggestion that this drug may increase mortality when used to treat PAD, Cortese told TCTMD that long-term follow up of patients will be conducted “even if all the studies performed in the coronary arena till now never gave

Sources

Cortese B. Drug-coated balloon vs drug eluting stent for small coronary vessel disease: 6-mo primary outcome of the PICCOLETO II randomized clinical trial. Presented at: TCT 2019. September 27, 2019. San Francisco, CA.

Disclosures

Cortese reports consulting for Abbott Vascular, Astra Zeneca, Kardia, Innova, Stentys, Daiichi Sankyo, Philips-Spectranetics, Reva, Bayer, and Cardinal; honorarium from Amgen, Stentys, Sanofi, B. Braun, Servier, and Alvimedica; and institutional research/grant support from AB Medica, St Jude, and Abbott.

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Balloon dilatation of pulmonary vein stenosis using PACLITAXEL eluting balloon: midterm result in an infant

A. Koch, M. Glöckler, C. Breuer, O. Toka, S. Dittrich

Introduction:

Pulmonary vein stenosis has an unfavorable outcome because neither surgical nor interventional therapy prevents restenosis.

According to promising results in pre-clinical studies, single infants with pulmonary vein stenosis have been treated by balloon dilatation using balloons coated with PACLITAXEL, an antimitotic agent from cancer therapy [1]. First results were encouraging, however, follow-up was cut off early in the two patients published so far, because both died within a few weeks [1,2].

Case Report:

A girl with univentricular heart, increased pulmonary perfusion, and mesocardia was treated by pulmonary banding at 3 weeks. Within the next weeks an increasing stenosis of the left sided pulmonary veins was suspected by echocardiography and confirmed by cardiac catheterization. Subsequently a Damus-Kaye-Stansel anastomosis, an aortopulmonary shunt, and a sutureless repair of the left sided pulmonary venous obstruction were performed at the age of 4 months.

At the age of 6 months, stenosis of the aortopulmonary shunt caused implantation of a 4mm coronary stent. Concurrently severe restenosis of the left pulmonary veins was diagnosed (fig.1) and treated by balloon dilatation.

6 weeks later, re-evaluation in the cath lab revealed severe restenosis, and again dilatation of the left pulmonary veins was performed now using PACLITAXEL coated balloons (5 and 6mm diameter).

This procedure was repeated at the age of 10, 13, and 16 months. 2 weeks after the last intervention (fig.2), surgical treatment with right sided Glenn anastomosis and left sided aortopulmonary shunt (5mm) was performed. 8 days after surgery the girl went home.

Out-patient follow-up after 6 weeks revealed the girl in a proper clinical condition with accelerated left-sided pulmonary venous return (Doppler Vmax 2.3m/s).

At the age of 22 months the girl was transferred to the cath lab for re-evaluation because of mildly increasing cyanosis. The left sided pulmonary vein showed moderate obstruction, and again re-dilatation was performed using a 6mm PACLITAXEL coated balloon (fig.3).

The right sided Glenn anastomosis was without obstruction, but there was a big anomalous venovenous connection between the superior vena cava and a paravertebral venous plexus draining to the inferior vena cava. The collateral was closed using an Amplatzer duct occluder (fig.4).

Conclusion:

Repeated balloon dilatation of pulmonary venous obstruction using paclitaxel eluting balloons may be useful in the interventional treatment of this frequently fatal condition. Although restenosis occurred also in our patient after the use of paclitaxel eluting balloons, the diameter of the treated vessel showed a reasonable increase, and the patient was able to undergo the next surgical step.

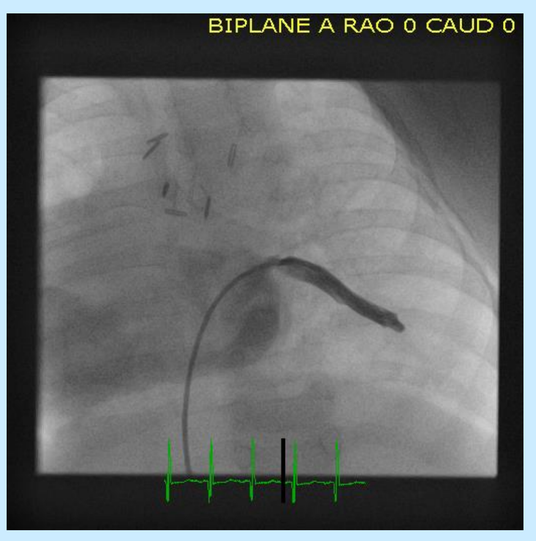

Fig.1: Pulmonary vein stenosis at the age of 6 months

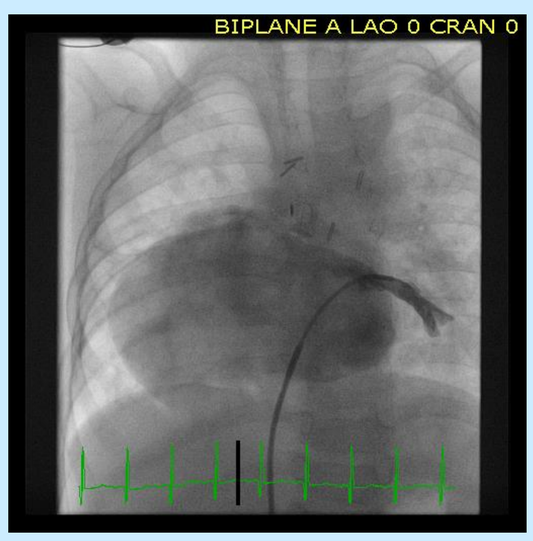

Fig.2: Pulmonary vein at the age of 16 months before surgery

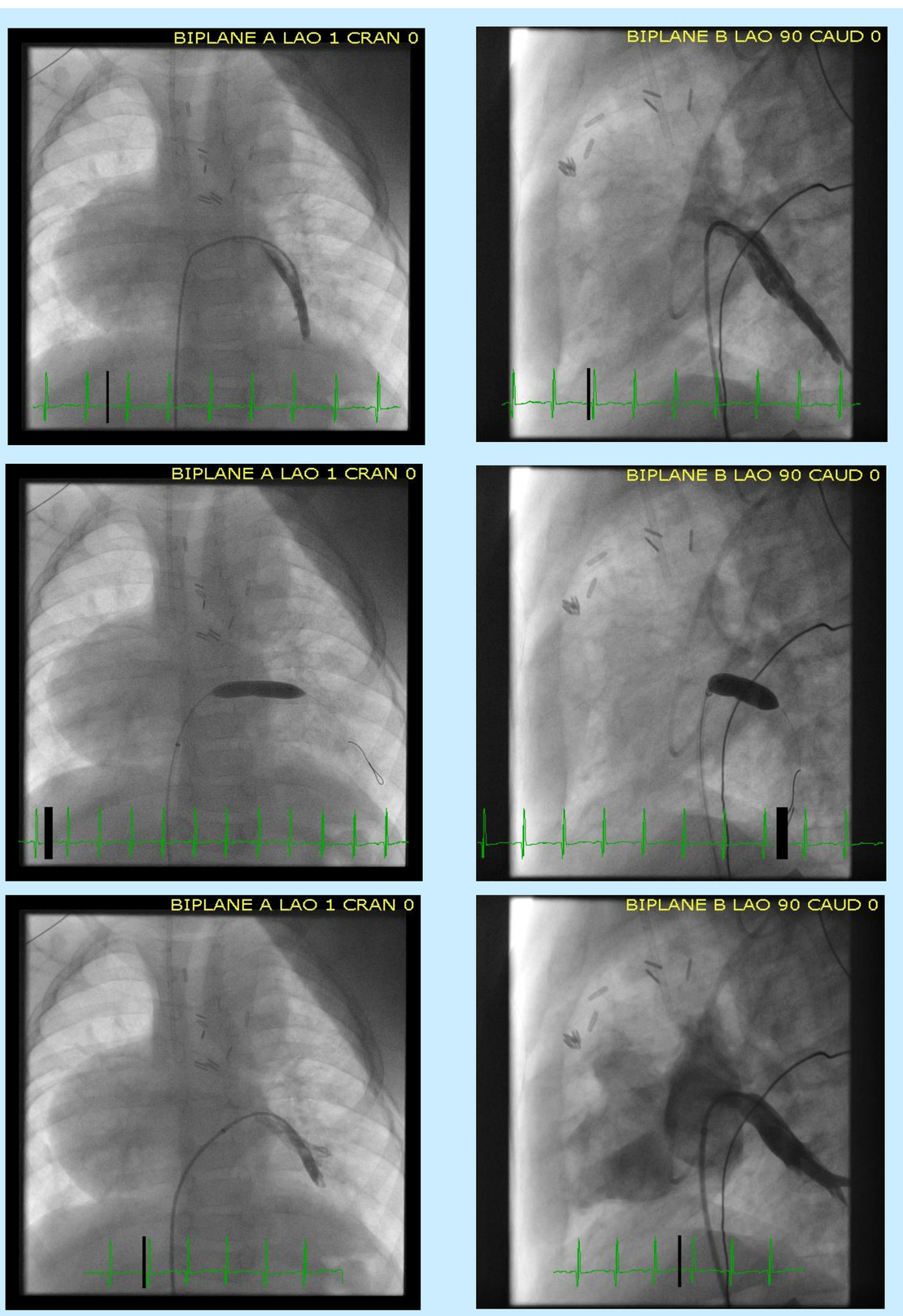

Fig. 3: Left pulmonary vein at the age of 22 months before (a,b), and after (e,f) redilatation using a 6mm PACLITAXEL coated balloon (c,d).

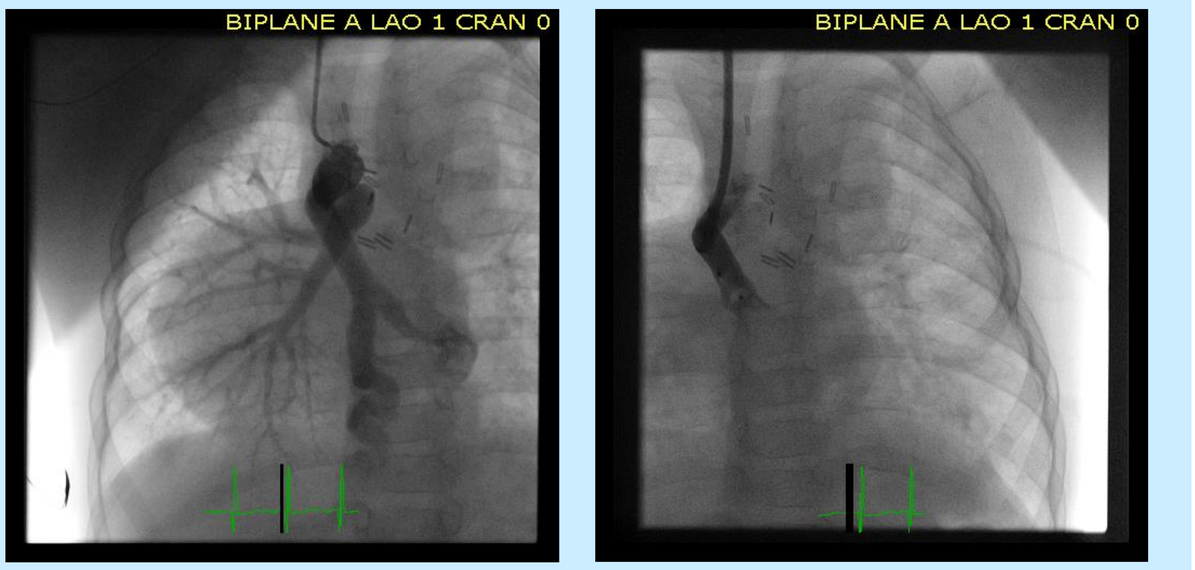

Fig. 4: Venovenous collateral (a), occlusion by Amplatzer duct occluder (b).

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