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Immediate and short-term performance of a novel sirolimus-coated balloon during complex percutaneous coronary interventions. The FAtebenefratelli SIrolimus COated-balloon (FASICO) registry☆

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ABSTRACT

Background and purposes: Drug-coated balloons (DCB) currently represent an alternative to drug-eluting stents (DES) for the treatment of in-stent restenosis and they are also variably used for small coronary vessel and bifurcation lesion management. All DCB variably elute paclitaxel as an anti-proliferative drug. The first sirolimus coated balloon (SCB) received the CE mark in 2016, but its clinical performance has not been shown yet.
Methods and results: FASICO in an all-comer registry of the first consecutive patients with at least one lesion treated with SCB between March and July 2016 at the first European centre that used this device. All patients were prospectively enrolled in a dedicated database. Primary endpoint was procedural success; co-primary endpoint was the rate of major adverse cardiac events at short-term follow-up. The 32 patients (34 lesions) enrolled had at least 6-month clinical follow up available. Forty-five percent had diabetes and indication to PCI was ISR in 47% of the cases. Lesions were always pre-dilated and device deployment was successful in all the cases. Procedural success was achieved in 100% of patients. We observed 3 cases of TLR at follow-up.
Conclusions: SCB shows high immediate technical performance and adequate short-term efficacy and safety. The ongoing EASTBOURNE registry will shed light on mid-and long-term performance of this device in an adequately powered population.

1. Introduction

Since the advent of the latest generation of drug-eluting stents (DES), percutaneous coronary interventions (PCI) have expanded their indications, and currently these devices are considered the standard revascularization treatment for *de novo* coronary lesions [1,2]. Although new generation DES have potent antiproliferative properties and provide excellent clinical and angiographic long-term results [1,2], they still imply some limitations, including an increased bleeding risk associated with the need for a prolonged dual antiplatelet therapy (DAPT) and the risk of late and very late stent thrombosis [3,4]. Moreover, given the increasing complexity of coronary interventions, the adoption of hybrid revascularization strategies are a valid alternative to a *solo*-DES PCI [5–7].

Drug-coated balloons (DCB) have been developed in recent years to overcome some of the DES limitations [8]. Their goal is to provide mechanical expansion of the stenosis combined with the release of an anti-proliferative drug, without leaving a foreign body. There is an established indication for the use of DCB in the treatment of in-stent restenosis [9] and they are also variably used in small coronary vessels and bifurcations [10–14]. Until 2016, all DCBs available in Europe eluted paclitaxel, a highly lipophilic drug with narrow therapeutic window.

In April 2016 a new sirolimus-coated balloon (SCB, Magic Touch®, Envision Scientific PVT, India), obtained the CE Mark. This device shares a new delivery system and is able to release an effective and well recognized anti-proliferative drug, but to this day it has not yet been adequately tested in contemporary-era PCI.

2. Methods

The FAtebenefratelli SIrolimus COated-balloon (FASICO) is an all-comer prospective registry of the first consecutive patients, who had at least one lesion treated with SCB between April and July 2016 at the first European center that had the device available for use after obtaining the CE Mark. The aim of the study was to demonstrate the acute performance and the 6-month efficacy and safety of this device in a real world, complex population.

☆ No conflicts of interest to declare related to this study.

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2.1. SCB: technical details

The device under investigation consists in a latest-generation monorail delivery system compatible with 5-Fr guiding catheters. The low-profile distal tip and the rigid hypotube, along with the technique of drug deposition, allow high deliverability and trackability. Available balloon sizes range between 1.5–4 mm in diameter and 10–40 mm in usable lengths.

The balloon is coated with sirolimus in a uniform manner through the use of a spray coating. The technology specifically designed for this device (Nanolutè®) consists in the encapsulation of sirolimus in a protective lipophilic package, which allows the diffusion and penetration into the arterial wall during balloon inflation, overcoming the low lipophilicity of sirolimus. This package consists of nano-sized drug particles of 100–300 nm diameter. The total dose of the drug corresponds to 1.25 mg/mm^2 of surface of the balloon, well within the therapeutic window of sirolimus.

Animal studies have shown that only 10% of the drug is lost during transit, then about 56% is released with the first balloon inflation, which should last 40–60 s; an additional 20% of the drug may be administered with an eventual 2nd inflation, while only 14% remains on the balloon.

The blood concentration reaches its peak within the following 30 min, and then disappears within 24 h, while tissue concentration is still detectable after 14 days. The drug persists on the vessel wall after the balloon inflation for 15–30 days; basically, the pharmacokinetic properties of this SCB reflect to the ones of latest-generation paclitaxel-coated balloons [15,19] (Fig. 1).

2.2. Study population

All types of clinical settings and coronary lesions were enrolled in this registry, including acute coronary syndromes, in-stent restenosis, long lesions and calcified vessels. We included all the attempted PCIs with SCB. The clinical and lesion complexity of the enrolled population reflect current population in Europe. The only exclusion criteria were vessel dimensions that exceeded those of the device tested, and those cases where we opted for another treatment strategy. All the patients treated with SCB entered a dedicated database and were followed up prospectively.

2.3. Study procedure

The procedure was performed according to international guidelines and local protocols. SCBs were inflated for a minimum of 30 s, but preferably for 60 s if they were well tolerated by the patient. Following local practice and the Italian GISE Position Document on DCB-PCI [16,17], we were committed to always carefully prepare the lesions and avoid stent implantation afterwards unless strictly needed. Lesion length and vessel reference diameter were assessed by visual estimation as during routine

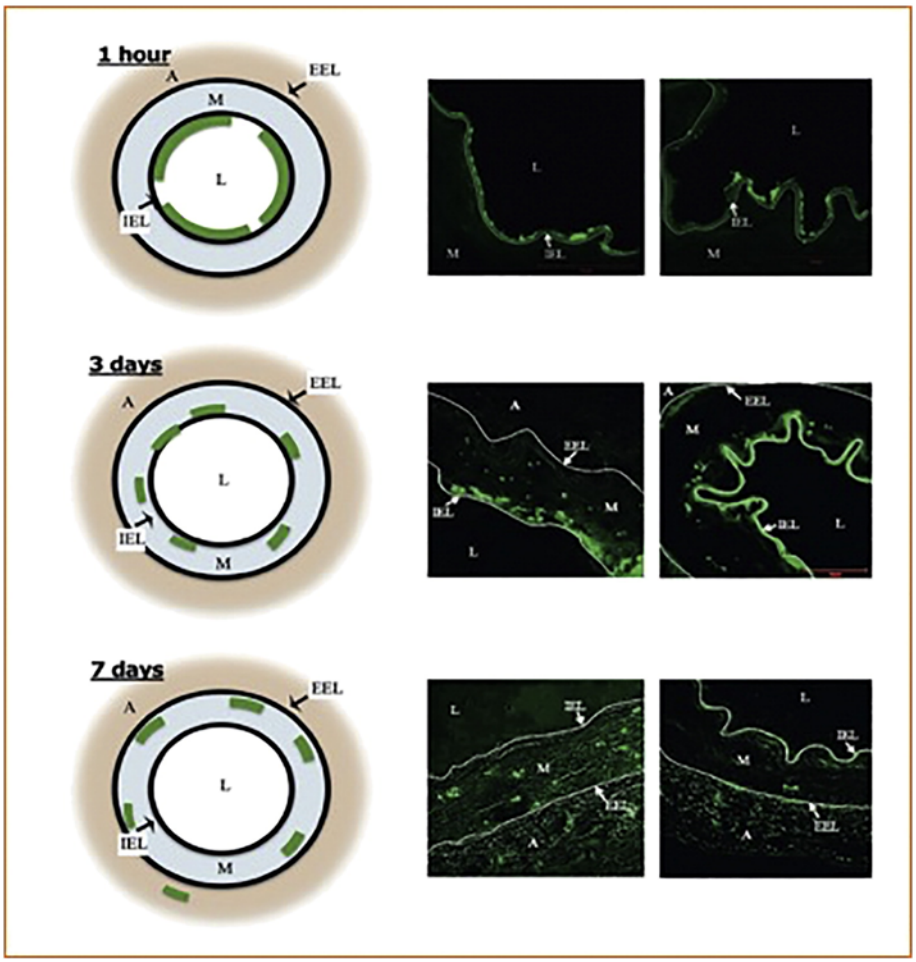

Fig. 1. Describes the temporal penetration of DTF-labeled sirolimus nanoparticles after drug-coated balloon inflation, as assessed by confocal microscopy. The left panels show a diagrammatic representation and the mid and right panels the actual cross-sectional images. At 1 h (upper panels), 60% to 70% of circumferential area was marked with DTF signal. No particle was seen below the internal elastic lamina. At 3 days (mid panels), 30% to 40% of circumferential area presented DTF signal. The majority of particles were below the internal elastic lamina (some positive signals deeper in media). At 7 days (lower panels), 30% to 40% of circumferential area had DTF signal. Particles primarily in deep media, with rare extension into adventitia. A: adventitia; EEL: external elastic lamina; IEL: internal elastic lamina; L: lumen; M: media. Reprinted from Eurointervention, P.A. Lemos et al. 2013 May 20;9(1):148–56, with permission from Europa Digital & Publishing.

Table 1
Baseline characteristics of the population.

Number of patients (n = 32)	
Males, n (%)	26 (81)
Arterial hypertension, n (%)	22 (69)
Diabetes mellitus, n (%)	11 (33)
Hyperlipidemia, n (%)	22 (69)
Smoker, n (%)	9 (28)
Stable coronary artery disease, n (%)	21 (66)
Acute coronary syndromes, n (%)	10 (31)
STEMI, n (%)	3 (9.3)

STEMI: ST-segment elevation myocardial infarction.

Table 2
Lesion characteristics of the population.

Lesion characteristics (n = 34)	
Target lesion:	
LAD, %	64.93
CX, %	13.86
RCA, %	21.21
ISR, n (%)	16 (47)
ISR previously treated with PCB, n (%)	11 (32.3)
De-novo lesions, n (%)	18 (53)
Lesion length, mean, mm (SD)	18.58 (8.4)
Reference vessel diameter, mean, mm (SD)	2.69 (0.54)
Bifurcation culprit lesion (side branch), n (%)	7 (20.6)
Percent lesion stenosis, mean, % (SD)	83.64 (13.8)
Degree calcification (moderate/severe), n (%)	11 (32.3)
Multi-vessel disease, n (%)	17 (50)

Legend: CX: left circumflex artery; ISR: in-stent restenosis; LAD: left anterior descendent artery; RCA: right coronary artery.

activity in our catheterization laboratory. As per local practice and expert consensus, all treated lesions were evaluated after at least 15 min before removing the guiding catheter for the assessment of potential acute vessel recoil [17]. A DAPT of at least 1 month was recommended in case of *de novo* lesion treatment and 3 months in case of ISR, unless longer DAPT was clinically indicated (*e.g.*, ACS) [16].

2.4. Endpoints

We individuated 2 primary endpoints for the current analysis. The first consisted in the immediate technical and clinical performance of this device in terms of procedural success, defined as final % diameter stenosis <50% with 3 TIMI flow and the absence of in-hospital adverse events. The co-primary endpoint was the rate of major adverse cardiac events (MACE), a total of cardiac death, myocardial infarction-MI, TLR at the longest available follow-up. MI was defined according to the universal definition [18]. TLR was defined as repeat PCI or coronary artery bypass grafting for the target segment or in the adjacent proximal or distal 5 mm segments. All patients enrolled had to have at least 6 months clinical follow up available.

3. Results

Between April and September 2016, a total of 521 PCIs were performed at our institution, and 32 patients, with 34 lesions treated or attempted with an SCB, were included in the current analysis. Twenty-six (83%) patients were males and 11 (35%) had diabetes mellitus. Table 1 describes the clinical characteristics of our population. The patients we treated with SCB represent a complex population. Notably, in half of the cases SCB was used for the treatment of in-stent restenosis (16 patients), mainly DES-restenosis (12 patients). Furthermore, 31% of the whole population was treated for failure of previous paclitaxel-coated balloon PCI (used for ISR).

Lesion characteristics are described in Table 2. Average lesion length was 18.58 mm (SD ± 8.44 mm), and mean reference vessel diameter 2.69 mm (SD ± 0.54 mm). All lesions were carefully pre-dilated using semi-compliant balloons. In one case we prepared the lesion with Rotablator (Boston Scientific, MA, USA) due to a high calcific burden (Fig. 2).

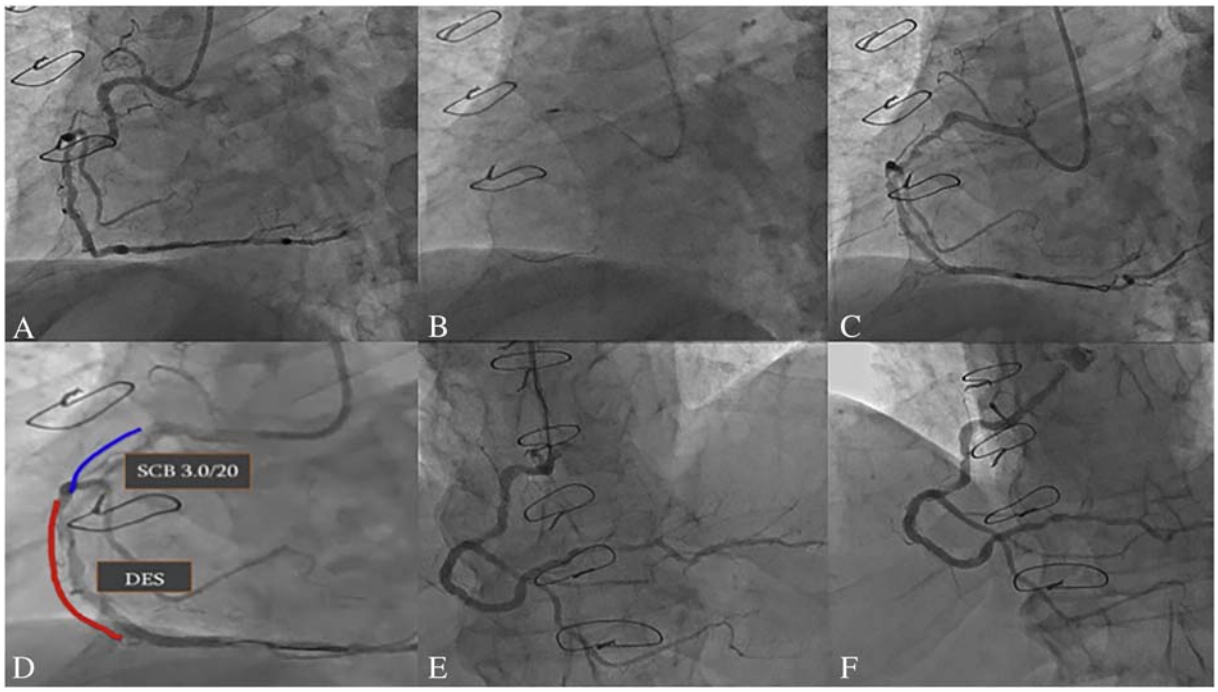

Fig. 2. Describes the management of a highly complex, calcific lesion of the right coronary artery (RCA)(A). First step consisted in atherectomy with Rotablator (B) and aggressive predilatation with different noncompliant balloons of increasing diameters up to 2.75 mm. After pre-dilatation, angiography showed multiple dissections in the proximal and mid portions (C). The strategy chosen was to implant one DES in the mid-distal RCA and to treat the proximal lesion with SCB (D). Final angiographic result (E). The angiographic follow-up after 4 months showed the persistence of a good result, with mild lumen gain the segment treated with SCB (F).

Table 3
Procedural characteristics.

SCB length, mean, mm (SD)	21.02 (4.7)
SCB diameter, mean, mm (SD)	2.6 (0.52)
Inflation time, mean, sec (SD)	50 (16.7)
Inflation pressure, mean, atm. (SD)	11.6 (4.73)
Minimal lumen diameter pre, mean, mm (SD)	0.39 (0.08)
Minimal lumen diameter post, mean, mm (SD)	2.20 (0.44)
Hybrid approach SCB + DES on the same vessel, n (%)	9 (26.5)
Hybrid approach SCB + stent on another vessel (same procedure), n (%)	5 (14.7)
TnI peak after PCI, average value, μg/l (SD)	40 (21.6)
Angiographic success, %	100
Procedural success, %	100

DES: drug-eluting stent; PCI: percutaneous coronary intervention; SCB: sirolimus-coated balloon.

The average device length used was 21.02 mm (SD ± 4.7 mm), with a diameter of 2.6 mm (SD ± 0.52 mm). Additional stent implantation was required in 3 cases (8.8%) for a flow-limiting major dissection. In all of these cases a new-generation DES was implanted. No intra-procedural complications or adverse events were observed. Procedural aspects are described in Table 3.

The primary study endpoint, procedural success, was obtained in 100% of the cases with no in-hospital complications. Clinical outcomes at follow-up are shown in Table 4.

The average clinical follow-up was 6.9 months (±1.7 months). During this period 3 patients had one MACE caused by TLR. In one case the patient experienced the recurrence of unstable angina 2 months after the index procedure for a critical restenosis of a DES restenosis, and was managed with a new angioplasty, this time with a paclitaxel-eluting DCB. The second patient experienced TLR caused by recurrent ISR of a BMS, where previous attempts with DES and paclitaxel-eluting DCB had failed. In this case the patient arrived with unstable angina after 3 months and we observed a 60% restenosis at angiography; OCT showed severe underexpansion of the DES that was treated with aggressive dilatation with noncompliant balloon at high pressures, and further SCB use. The patient remained asymptomatic in the following 4 months. The last TLR occurred in a patient treated with an SCB for chronic total occlusion of a previously implanted DES; the patient came back after 5 months with positive stress test, and angiography showed a recurrent total occlusion. This lesion was treated with additional DES implantation, for the impossibility to obtain a satisfactory lesion preparation despite the use of scoring balloon predilatation. During the follow up, we did not register any MI or death in the study population.

4. Discussion

The main finding of the all-comer FASICO registry is that the investigated SCB is a safe and effective treatment option at short-term follow up, in a real world, complex population of coronary artery disease patients. The main findings of our registry are the following:

1) Differently from other previous technologies [8], the technical properties of this device allow the treatment of complex coronary lesions with high procedural success. In fact, deliverability and trackability were adequate and allowed complete device deliverability and procedural success;
2) The 6-month data of this population showed a good clinical outcome considering the highly complex population enrolled.

Table 4
Clinical follow up (average: 6.9 ± 1.7 months).

DAPT ongoing, n [%]	10 [31.6]
All-cause death, n [%]	0
Cardiac death, n [%]	0
Target lesion revascularization, n [%]	3 [9.4]
MI, n [%]	0
MACE, n [%]	3 [9.4]

Legend: MACE: major adverse cardiac events; MI: myocardial infarction.

A specific mention should be done regarding clinical outcome. During the follow up, we observed 3 adverse events related to TLR. The occurrence of these revascularizations may be explained by the following considerations. First, this is a complex population, with almost half of the patients that already experienced failure of a previous device (ISR was the cause for half of the procedures); furthermore, 1/3 of the patients enrolled received a re-PCI for failure of paclitaxel-eluting DCB. Finally, one third of the lesions treated (32.4%) had a moderate-to-severe degree of calcification (Fig. 2), in these cases the main reason for shifting from a DES-PCI. Interestingly, in 34% of the cases the high complexity of the lesions treated (Medina type 1,1,1 bifurcations, proliferative ISR) required a hybrid approach with DES + SCB.

It is important to underline how the three TLR observed occurred in patients where second-generation DES or PCB had already failed. Specifically, in one case we observed at the OCT a severe under-expansion of a DES previously implanted. Another TLR occurred in a patient diagnosed with nickel allergy. Of note, no adverse events were observed in patients treated for *de novo* lesions or BMS restenosis.

4.1. Study limitations

This study has some evident limitations: it is a small, single center registry, with no centralized event adjudication, showing the immediate and short-term performance of a new device. On top of the small population enrolled and the relatively short follow up, there is no angiographic follow up, a required item for the complete assessment of a new coronary device. Despite of some importance that we felt to present this preliminary experience with a novel device, we truly believe that more data should be provided before this SCB will enter the routine practice. The ongoing European, prospective, multicenter EASTBOURNE registry, that will enroll around 1000 patients with any type of coronary artery disease, will add more information on the topic.

5. Conclusions

The DCB investigated in this registry is the first one eluting sirolimus and approved for human use in Europe. This device was shown to be a safe and effective alternative to currently used DCB at short-term follow up, in a real world, complex population.

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Conflict of interest statement

The authors have no conflicts of interests to declare.

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