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Angiographic performance of a novel sirolimus-coated balloon in native coronary lesions: the FAtebenefratelli SIrolimus COated NATIVES prospective registry

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Aims **To evaluate the angiographic performance of a novel sirolimus-coated balloon (SCB) in de novo coronary lesions.**

Methods **Out of an all-comer prospective registry of patients treated with the SCB at our center from April 2016 to September 2017, we selected those treated for a de novo stenosis on a native vessel, with a scheduled angiographic control at at least 4 months after the index procedure. We performed a centralized, blinded core-lab adjudicated quantitative coronary angiography analysis. Primary endpoint was late lumen loss. Secondary endpoints were binary restenosis and target-lesion revascularization.**

Results **A total of 27 patients with native coronary arteries treated with SCB and with angiographic follow-up entered the study; seven patients were excluded because a stent was implanted at the lesion site during the index procedure. The degree of calcification (assessed with coronary angiography) was high in six patients (30%) and the average lesion length was 20.52 ± 6.88 mm. The reference vessel diameter was 2.32 ± 0.44 mm and the percentage diameter stenosis was 67 ± 12. Procedural success was obtained in all patients. After a median of 6.6 ± 2.5 months, late lumen loss was 0.09 ± 0.34 mm and the percentage diameter stenosis was 31 ± 18. We observed two cases (10%) of binary restenosis which underwent subsequent target-lesion revascularization: in one a drug-eluting stent was implanted, whereas the other patient was treated with paclitaxel-coated balloon. No myocardial infarction or death was observed during follow-up.**

Conclusion **The use of a novel SCB in native coronary arteries was associated with good angiographic outcome at 6-month follow-up.**

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Keywords: drug-coated balloons, native coronary artery disease, percutaneous coronary intervention, sirolimus-coated balloons

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Introduction

In 2018 drug-eluting stents (DESs) were the mainstay of revascularization treatment for the vast majority of coronary lesions.[1,2] Although new-generation DESs provide excellent clinical and angiographic long-term results compared with previous generations,[1,2] they still suffer from some limitations, including the risk of late and very late stent thrombosis[3,4] and the subsequent need for a prolonged dual antiplatelet therapy (DAPT).[5]

In recent years, drug-coated balloons (DCBs) gained increasing popularity among interventional cardiologists, thanks to fast-paced technological development. The rationale beyond performing an angioplasty with a DCB relied on the concept of treating the coronary artery through a mechanical expansion of the stenosis and the administration of antiproliferative drugs to the vessel wall, without the need for the implantation of a scaffold or any other foreign body.[6,7] These theories received support from subsequent studies, and nowadays these novel devices have an established indication for the treatment of in-stent restenosis[8] but they are also variably used in small coronary vessels and bifurcation lesions.[9–13] Moreover, the availability of these new devices allowed the adoption of hybrid revascularization strategies as a valid alternative to a solo-DES percutaneous coronary intervention (PCI), because of the increasing complexity of coronary interventions.[14–16]

The key elements determining the performance of a DCB are the drug adsorbed on its surface, and the capability of the device to deliver it to the vessel wall. Many technologies were adopted from the consistent experience with DES. Here, derivatives of rapamycin (like everolimus, sirolimus and zotarolimus) replaced paclitaxel as the antiproliferative drug of choice, due to superior results both in terms of efficacy (reduction of restenosis) and safety (reduced toxicity, larger therapeutic interval). Indeed, paclitaxel suffered the main drawback of having a narrow therapeutic range, with a small gap between therapeutic and toxic blood concentrations. However, until 2016 available DCBs consisted only of paclitaxel-eluting balloons, as the high lipophilia of the drug allowed it to coat the polymeric surface of the balloon easily and to be transferred into the vessel wall during balloon inflation. Despite

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its theoretically improved clinical profile, sirolimus had a major drawback in its hydrophilic nature, which made adsorption to the balloon surface and effective elution to the vessel wall difficult. Thus, major effort was put in technological advancements, and in April 2016 Magic Touch (Envision Scientific PVT, Hazira, India) was the first sirolimus-coated balloon (SCB) receiving the CE mark and entering the market. Novel coating and delivery technologies allowed this device to overcome the aforementioned limitations of sirolimus.[17,18] The FASICO (FAtebenefratelli SIrolimus COated) registry reported the first clinical results of this new device in a clinical setting.[19] From this registry, we selected the patients which were treated at our center with the SCB and with scheduled angiographic follow-up. Here, we report the primary outcome of the FASICO NATIVES registry.

Methods

The FASICO registry enrolled all consecutive patients treated with SCB at our institution from April 2016 to July 2016, then the enrollment for FASICO NATIVES was extended up to May 2017, due to the need for stronger data on the device from a larger population. Out of these patients, the FASICO NATIVES registry prospectively enrolled all patients treated in a de novo lesion, who had a scheduled angiographic control between 4 and 8 months after index procedure. The reasons for the angiography were either a programmed control due to the complexity of index procedure, or a staged procedure. Exclusion criteria were in-stent restenosis, unavailability to undergo control angiography, the occurrence of an acute coronary syndrome, angina or silent ischemia.

A centralized, blinded core-lab adjudicated quantitative coronary angiography (QCA) analysis was performed for every procedure. Primary endpoint was late lumen loss (LLL) at the angiographic control, defined as the difference in minimal lumen diameter (MLD) between the immediate post-PCI result and the angiographic follow-up. Secondary endpoints were binary restenosis and target-lesion revascularization (TLR) rates. Binary restenosis was defined as diameter stenosis at least 50% within a previously treated segment on follow-up QCA. 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 basal and final angiograms were taken after a bolus of intracoronary nitroglycerin.

Technical success was defined as final diameter stenosis less than 50% with 3 TIMI flow. Procedural success was defined as technical success and the absence of in-hospital adverse events post-PCI. Both the FASICO and the FASICO NATIVES registries received internal institutional review board approval.

Study procedure

The procedures were 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. According to local practice and the Italian GISE Position Document on DCB-PCI,[20,21] operators always performed predilations of the lesions with semicompliant balloons, to obtain its adequate preparation. Stent implantation was considered only as a bailout strategy, in case of inadequate results (i.e. acute recoil of the vessel) or significant ($\geq$type C) vessel dissection. Lesion length and reference vessel diameter (RVD) were assessed by visual estimation as during routine activity in our catheterization laboratory, and devices were chosen accordingly, to avoid geographical mismatch. In case of unclear severity of stenosis, additional tests were possible according to physician's preference (fractional flow reserve, optical coherence tomography, intravascular ultrasound). As per local practice and expert consensus, operators performed a final evaluation of all treated lesions after at least 15 min, to detect potential acute vessel recoil.[20] Patients received DAPT for at least 1 month after the procedure, unless other conditions required a longer duration.[21] All patients were informed and signed a dedicated consent form before entering this registry.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD. Categorical variables are presented as counts and frequencies (%). In case of normal distribution of variables, paired *t* test was used. In case of nonnormal distribution, data were analyzed with Friedman and Wilcoxon rank sum tests. *P* values were two-tailed, with statistical significance set at 0.05. SPSS for Macintosh (version 23; IBM, Armonk, New York, USA) was used for statistical calculations.

Results

The overall number of enrolled patients in the FASICO registry was 85. Among these patients, 27 were treated for native coronary vessel disease and had an angiographic follow-up available in the prespecified timeframe. Of these, seven patients were excluded due to a stent implantation at the target lesion during the index procedure, six due to major dissection, one due to significant residual stenosis. Therefore, 20 patients were viable for final analysis.

Baseline characteristics of the study population are reported in Table 1. The mean age was 67.06 $\pm$ 9.82 years, 85% of the patients were men, and hypertension and dyslipidemia were present in 80% of them; 35% of the patients had a history of diabetes mellitus and 45% had a previous myocardial infarction (MI), describing a high-risk population; 95% of the patients had a history of previous revascularization, either with PCI or coronary artery bypass graft. The main indication for the index procedure was stable coronary artery disease (80% of the

Table 1 Characteristics of the study population at the baseline

Age (years)	67.06 ± 9.82
Males, *n*	17 (85%)
Arterial hypertension, *n*	16 (80%)
Hyperlipidemia, *n*	16 (80%)
Diabetes mellitus, *n*	7 (35%)
Insulin-dependent diabetes mellitus	1 (14.29%)
Noninsulin-dependent diabetes mellitus	6 (85.71%)
Current smoker, *n*	6 (30%)
Clinical presentation	
Stable coronary artery disease, *n*	16 (80%)
Acute coronary syndrome, *n*	4 (20%)
Previous PCI/CABG, *n*	19 (95%)
Previous myocardial infarction, *n*	9 (45%)
Left ventricle ejection fraction (%)	51.28 ± 8.73

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

cases). No procedures were performed in patients with a ST-elevation MI.

Angiographic characteristics of target lesions during the index procedure are described in Table 2. Target vessels were equally distributed, with a slight prevalence for the left anterior descending artery (40%). Target lesions were complex (type B2 or C) in two-thirds of the patients and with a high degree of calcification in one-third. In one case, a chronic total occlusion was present. Average lesion length was 20.52 ± 6.88 mm. RVD was 2.32 ± 0.44 and MLD 0.77 ± 0.39 mm. Percentage diameter stenosis was 68 ± 12 (Table 3).

All lesions were treated according to standard recommendations regarding the use of DCBs, explained in the 'study procedure' section.[20,21] After treatment with the device, MLD was 1.68 ± 0.48 mm ($P < 0.001$ vs. baseline MLD) and percentage stenosis was 26 ± 14. Acute gain of vessel diameter was 0.91 ± 0.33 mm. In three cases a residual, not flow-limiting, minor dissection was present at the end of the procedure. Procedural success was achieved in all patients. No major adverse events occurred during the index procedure and in-hospital stay.

Table 2 Baseline characteristics of the treated lesions and index procedure

Target lesion	
LAD	6 (30%)
LCX	6 (30%)
RCA	8 (40%)
Lesion length (mm)	20.52 ± 6.88
Reference vessel diameter (mm)	2.32 ± 0.44
Lesion stenosis (%)	67.64 ± 11.78
Minimal lumen diameter (mm)	0.77 ± 0.39
Complex lesion (type B2/C), *n*	14 (70%)
Calcification degree (moderate/severe), *n*	7 (35%)
Multivessel disease, *n*	17 (85%)
Bifurcation (target lesion at side branch)	2 (10%)
Need for rotational atherectomy, *n*	1 (5%)
SCB length (mm)	23.89 ± 6.98
SCB diameter (mm)	2.25 ± 0.46
SCB inflation time (s)	60.56 ± 8.02
SCB inflation pressure (atm)	14.56 ± 11.86

Reference vessel diameter, minimal lumen diameter, lesion length and percentage stenosis evaluated with quantitative coronary angiography analysis. LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; SCB, sirolimus-coated balloon.

Table 3 Angiographic outcomes of treated lesions after the index procedure (column 3) and at the angiographic follow-up (column 4)

	Baseline	Postprocedure	Follow-up
Lesion stenosis (%)	67.64 ± 11.78	25.86 ± 14.31	31.01 ± 17.85
Minimal lumen diameter (mm)	0.77 ± 0.39	1.68 ± 0.48	1.59 ± 0.59
Lumen gain vs. baseline (mm)	–	0.91 ± 0.33	0.82 ± 0.38
Late lumen loss vs. postprocedure (mm)	–	–	0.09 ± 0.34

Reference vessel diameter, minimal lumen diameter, lesion length and percentage stenosis evaluated with quantitative coronary angiography analysis. Difference in MLD was significant between baseline and post-PCI ($P < 0.001$). Difference was significant between control values and baseline ($P < 0.001$), too, but it was NS between post-PCI and angiographic control. MLD, minimal lumen diameter; PCI, percutaneous coronary intervention.

DAPT was prescribed according to guidelines of the European Society of Cardiology, consisting of at least 1 month of DAPT for patients with stable coronary artery disease (CAD) and 12 months in the case of acute coronary syndromes. Clopidogrel was used in the case of stable CAD (80%), ticagrelor in the case of acute coronary syndromes (20%).

Angiographic follow-up occurred after a median of 6.6 ± 2.5 months. At the follow-up QCA, the mean MLD was 1.59 ± 0.59 mm ($P < 0.001$ vs. baseline MLD) and the mean percentage diameter stenosis was 31 ± 18. Compared with the immediate results of the index procedures, LLL was 0.09 ± 0.34 mm (Figs. 1 and 2). Compared with an immediate post-PCI result, there were no significant differences (MLD post-PCI 1.68 ± 0.48 mm, MLD at control 1.59 ± 0.59 mm, $P = 0.3$). We observed two cases (10%) of binary restenosis that required subsequent TLR: in one case a DES was implanted and in one we performed angioplasty with a paclitaxel-coated balloon. No in-hospital complications occurred. No cases of MI or deaths were observed during follow-up.

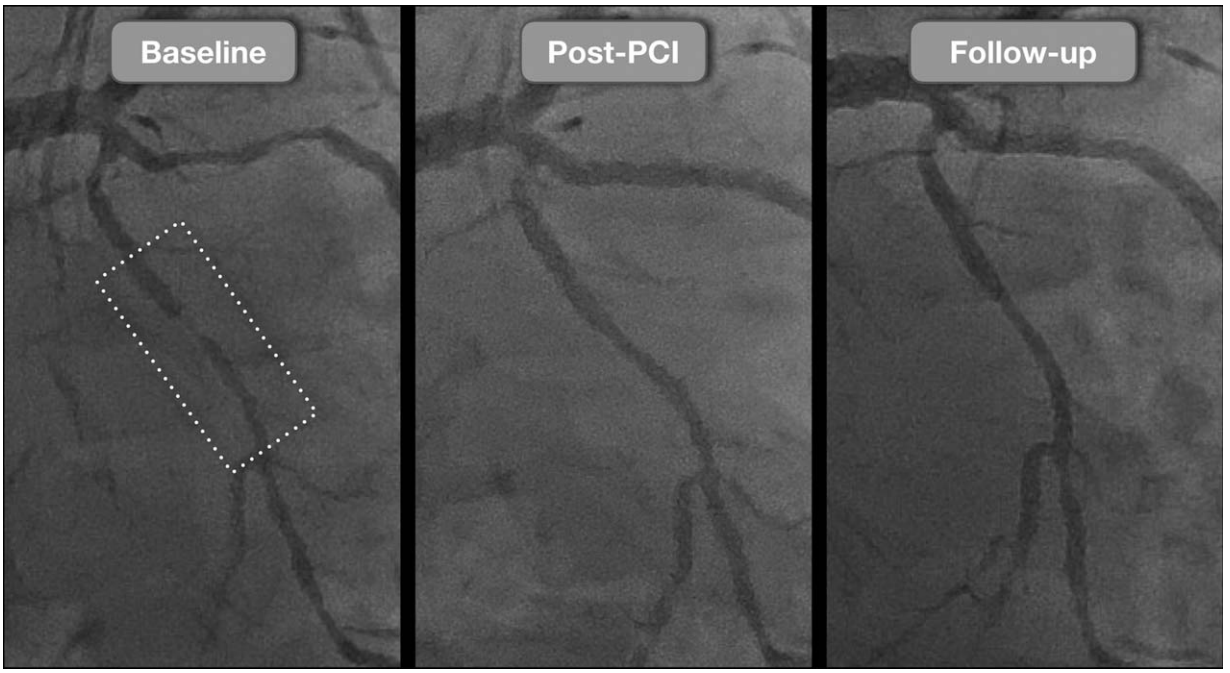
At the time of follow-up, eight patients were still on DAPT. There was no correlation between DAPT discontinuation and angiographic outcome, as the cases of binary restenosis were observed during the first 6-month period and still on DAPT (at 2 and 6 months, respectively, the first being in a patient with stable CAD on clopidogrel, and the second being a patient treated for a NSTEMI, still on ticagrelor).

Even though the sample size was small, logistic regression analyses were performed to determine whether any variables were associated with a better or worse outcome, but no specific determinant was found.

Discussion

The current prospective angiographic study in the setting of de novo coronary artery stenosis confirmed and expanded the results of the FASICO registry.[19] In that study, immediate and mid-term clinical outcomes (both in de novo coronary artery disease and in-stent restenosis)

Fig. 1



Example of the angiographic results of the sirolimus-coated balloon. At the baseline a significant de novo stenosis of the left circumflex artery was detected (left panel). The lesion was treated with a predilation with a semicompliant balloon and a sirolimus-coated balloon. The central panel shows the immediate good result of the angioplasty. An angiographic control at 8 months (prescheduled assessment) confirmed the good outcome of the procedure (right panel).

were favorable and similar to traditional paclitaxel-coated balloons in terms of safety and efficacy. This study provides the first data on 6-month angiographic results, confirming the positive outcomes of the device, which therefore seems comparable with current similar therapeutic options.[6,7] Noteworthy, these results were obtained in a real-world, complex population of patients with coronary artery disease.

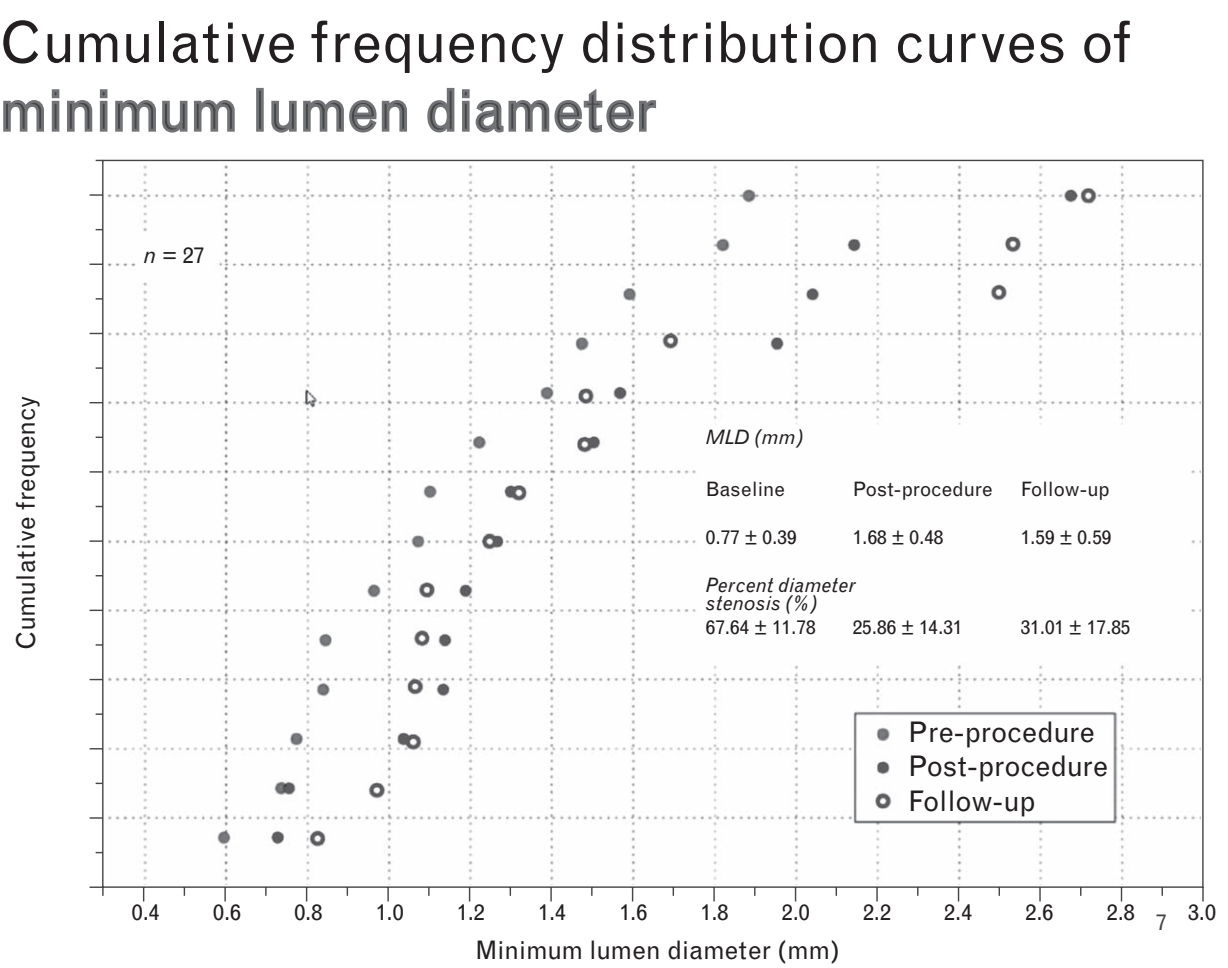
Even though the current common indication for the use of DCB is the treatment of in-stent restenosis, the SCB achieved good outcomes also in a setting of naïve coronary artery lesions. DES have the strongest indication for the treatment of these types of disease, but the use of a DCB allows avoiding the permanent deployment of a layer of metallic struts in the vessel wall, especially in small coronary vessels such as those treated in this study, in which the average vessel diameter was 2.3 mm: these vessels are indeed more prone to thrombosis or restenosis after stenting. Moreover, naïve lesions were the perfect setting to assess the immediate and late angiographic results of this SCB, without the risk of interferences from previous treatments.

Three cases of minor dissections were recorded at the end of the index procedures and were left untreated. However, at follow-up, the vessels appeared to have healed completely, with no residual flaps. This effect may be due to the slow effect over time of the drug eluted by the balloon, which may have contributed to a progressive restoration of the vessel wall. The same phenomenon may underlie the good results of SCB use in one patient after rotational atherectomy. Rotablation is known to cause extensive damage to the vessel wall, and stenting is the common treatment to prevent further complications. In this case, SCB provided good early and late angiographic results. The isolated report is insufficient to draw any conclusion, but it may be considered as hypothesis-generating.

We discovered two cases of binary restenosis requiring TLR in this study. Possible causes of restenosis may have been the high complexity of treated lesions, with a significant rate of moderate-to-severe calcifications, in patients with a heavy burden of cardiovascular risk factors, which may lead to a significant progression of coronary artery disease.

The use of DCB for the treatment of native coronary vessels is growing, with some evidence already available[22,23] and yet more to come, like the BASKET SMALL 2 and PICCOLETO 2 studies, whose results will be presented in the next few months. The chance of leaving a small coronary vessel without a stent implanted but with an efficacy similar to the one provided by DES is intriguing and should be considered, especially in patients with long lesions or at high risk of bleeding.

Fig. 2



Minimum lumen diameter change before the procedure, after and at 6-month angiographic follow-up. In about half of the cases a lumen enlargement can be detected.

Another interesting option could be the chimeric therapy of DES + DCB in long lesions, considering the high risk of in-stent restenosis and stent thrombosis in small vessels with long-stented segments.[3,4]

Another interesting discovery of this study is the lumen gain described by the QCA in about half of the patients (Fig. 2), an effect which has been already described with paclitaxel-coated balloons.[22,24] It is hard to go deeper in discussing this finding due to the limited population enrolled; however, this is an intriguing discovery that should be better investigated.

The results of this study confirm the effectiveness of SCBs for the treatment of de novo coronary lesions. These results add new evidence to support the adoption of this device as an effective alternative or a synergistic therapeutic option to traditional DES and paclitaxel-coated balloons. However, new studies are needed to make some strong recommendations on this topic. Currently, the prospective thE All-comers Sirolimus-coaTed BallOon eURopeaN rEgistry registry is enrolling patients in eight countries and 29 centers. The aim of this registry is to reach a target all-comer population of 1500 patients with any type of coronary artery disease and to follow it up clinically over a long-term period.

Study limitations

The current study has some evident limitations: it is a small, single center registry, with a limited sample size. Moreover, the indications for doing control angiography were different, although we excluded those patients who had recurrence of symptoms or myocardial ischemia. Third, we do not have a comparison arm. Finally, mid-term angiographic data represent significant progress compared with the short-term clinical follow-up of the previous studies; however, there is a need for longer follow-up with a larger sample and multiple study centers.

Conclusion

In conclusion, this prospective study with consecutive patients affected by small coronary artery disease treated with a novel SCB shows how this treatment is effective in maintaining good vessel patency at angiographic follow-up, with interesting signs in terms of late lumen gain.

Perspectives

In this registry, the first SCB approved for human use showed good outcomes in a setting of de novo coronary artery lesions, at a mid-term angiographic follow-up, both in terms of efficacy and safety. In a real-world, high-risk population with complex coronary artery lesions, this device was shown to offer similar results to those reported for currently used paclitaxel-coated balloons in similar settings.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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