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Clinical performance of a novel sirolimus-coated balloon in coronary artery disease: EASTBOURNE registry

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Aims **The purpose of the EASTBOURNE registry is to evaluate the immediate and long-term clinical performance of a novel sirolimus-coated balloon (SCB) in a real-world population of patients with coronary artery disease. We here present the prespecified interim analysis after the enrollment of the first 642 patients who obtained 1-year clinical follow-up.**

Methods **EASTBOURNE is a prospective, international, multicenter, all-comer investigator-driven clinical registry, which is enrolling consecutive patients treated with SCB at 42 European and Asiatic centers. Primary study endpoint is target-lesion revascularization (TLR) at 12 months. Secondary endpoints are procedural success and major adverse cardiac events through 36 months.**

Results **Diabetes mellitus was present in 41% of patients. Acute coronary syndrome was present in 45% of patients and de novo lesions were 55%; 83% of the in-stent restenosis (ISR) patients had drug-eluting stents restenosis. Lesion predilatation was performed in 95% of the cases and bailout stenting occurred in 7.5%. So far, 642 patients have a complete 12-month follow-up. TLR occurred in 2.5%, myocardial infarction in 2.3%, total death in 1% and major adverse cardiac events in 5.8% of patients. A prespecified analysis of comparison between ISR and de-novo lesions showed a significantly higher occurrence of TLR in the ISR population (5.4 vs. 0.2%, $P = 0.0008$).**

Conclusion **The current interim analysis of 12-month follow-up of the EASTBOURNE registry shows good immediate performance and an adequate and encouraging safety profile through 12 months for this novel SCB.**

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Introduction

The possibility of leaving no trace after a successful percutaneous coronary intervention (PCI) (namely, not implanting a prosthesis) may be somewhat appealing and potentially reduce adverse events in the long-term. Following this philosophy, in the last decade a number of bioresorbable scaffolds and several generations of drug-coated balloons (DCB) underwent dedicated clinical programs and received the CE mark for commercialization in Europe. In parallel, many improvements have been pursued to improve the quality of drug-eluting stents (DESs), which now share a nonthrombogenic (or no) polymer, safer drugs and thinner metal struts. So far, DESs are considered the gold-standard treatment for any type of PCI. On the other hand, the complexity of coronary interventions has substantially increased in the last decade; therefore, to reduce the number of stents to be implanted and keep the thrombotic risk low, newer strategies including hybrid therapies (DES + DCB) represent nowadays an alternative to a *solo*-DES PCI. If all DCB marketed in Europe since 2007 invariably eluted paclitaxel, in 2016 the first DCB eluting sirolimus (Magic Touch, Concept Medical, India) entered the European market. To this day, the performance of the sirolimus-coated balloon (SCB) in a wide series of patients affected by coronary artery disease has not been evaluated yet in an adequately powered clinical study.

Methods

Study design and population

The EASTBOURNE registry (NCT03085823) is a prospective, multicenter, investigator-driven clinical registry aiming to enroll a real-world, all-comer population of

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2000 patients at 42 interventional cardiology centers in Europe and Asia (Fig. 1). To participate in the study, all centers had to certify adequate experience of DCB treatment, which consisted of the use of at least 30 DCB/year in the last 5 years, for any investigator participating in the study.

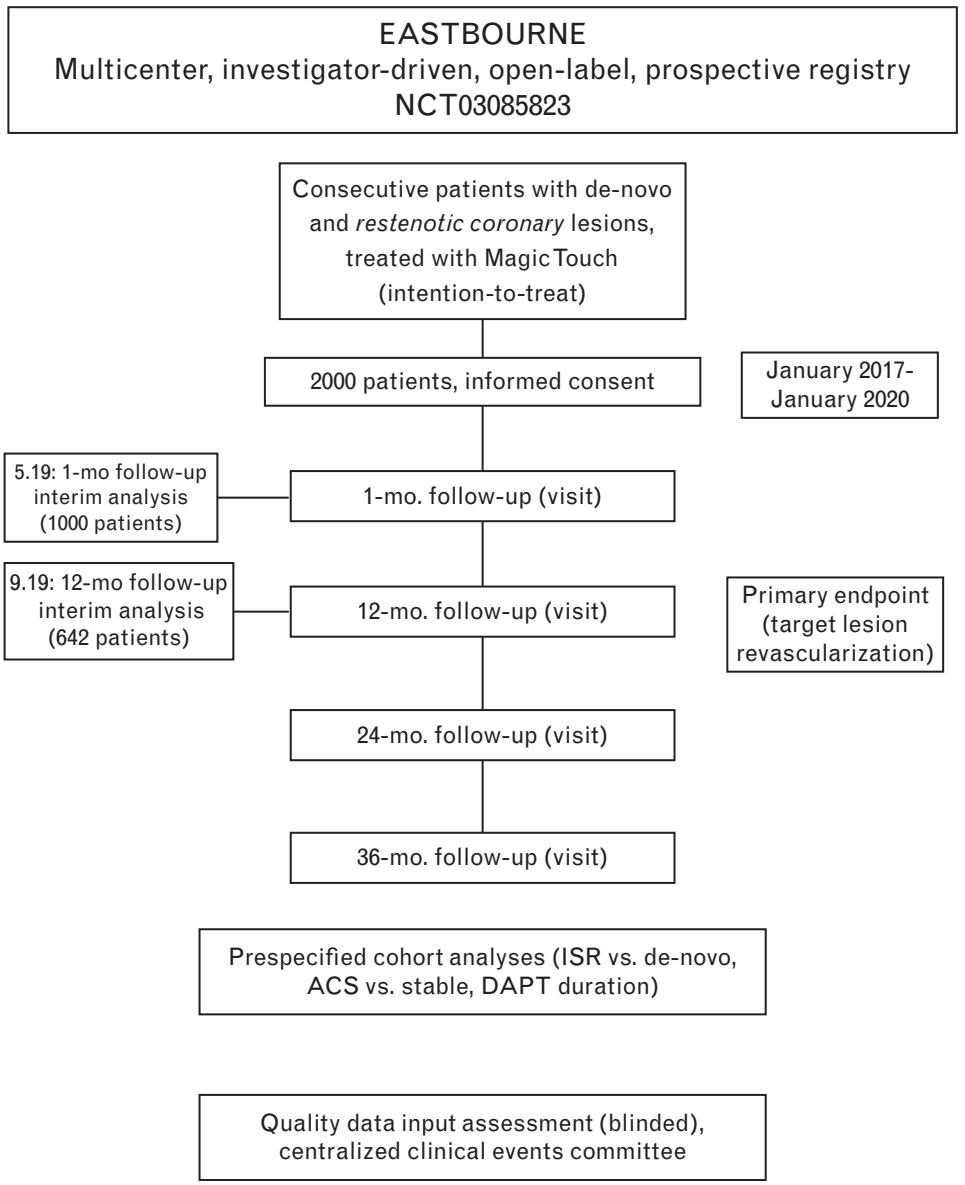
The aim of this registry is to observe and evaluate the performance of the SCB Magic Touch for the treatment of any type of coronary lesions, including native-vessel disease and in-stent restenosis (ISR).

Inclusion criteria are age more than 18 years, and all the spectrum of coronary artery disease with clinical indication for PCI, including patients with stable angina, silent ischemia and acute coronary syndromes.

Exclusion criteria are one or more of the following: patients with known (and untreatable) hypersensitivity or contra-indication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, sirolimus or contrast media; target lesion/vessel with any one of the following characteristics:

(1) Unsuccessful predilatation of the target lesion, with persisting residual stenosis more than 50%.
(2) Severe calcification of the target vessel, either at the lesion site or proximal to the lesion.
(3) Highly tortuous culprit vessels.

Fig. 1



Consort diagram of the EASTBOURNE registry.

(4) Visible thrombus at the lesion site, not treatable with manual aspiration.

The decision whether to use the DCB or any other treatment strategy was left at the operator's decision.

Device description

The Magic Touch – SCB is the first CE-marketed DCB eluting sirolimus, thanks to dedicated nanocarrier technology. Drug nominal dose on a 3.0/15-mm balloon is 180 μg (~1.27 μg/mm^2); sirolimus is encapsulated in a phospholipid bilayer working as a drug carrier and in nanocarrier configuration. The device is available in lengths from 10 to 40 mm and in diameters from 1.50 to 4.00 mm. The delivery system is a semicompliant coronary balloon with low tip profile and nanocarriers are coated onto a hydrophilic coated surface of the balloon. The surface of the balloon, on contact with blood forms microchannels by a wetting mechanism, which upon inflation delivers the drug faster once it has reached the lesion site. The balloon is compatible with 5-Fr guiding catheters. Preliminary data showed how the SCB due to its unique coating does not leave particulates downstream and is not associated with distal embolization.[1]

Procedure

The PCI procedure is performed according to current standard international guidelines. During the procedure, intravenous heparin (70–100 U/kg) is administered after sheath insertion to maintain an activated clotting time of more than 250 s (or >200 s if glycoprotein IIb/IIIa inhibitors are used, at the operator's discretion). Regarding the antiplatelet treatment, aspirin 100–325 mg is given prior to the procedure; a loading dose of ticagrelor 180 mg, prasugrel 60 mg or clopidogrel 300 mg (600 mg in case the procedure is scheduled within 2 h) is administered prior to the procedure, depending on the clinical presentation of the patient. After the procedure, all patients receive aspirin (75–100 mg) daily indefinitely, and one of either clopidogrel 75 mg, ticagrelor 90 mg × 2 or prasugrel 10 mg, which is prescribed for a minimum of 1 month (6 months are suggested in case of additional stent implantation). In patients presenting with ACS, the second antiplatelet is prescribed according to the clinical presentation and following international guidelines.

Since lesion preparation is mandatory, to obtain an adequate result before DCB use, investigators are committed to using any type of device deemed appropriate to obtain this goal, including semi or noncompliant balloons, atherectomy, scoring balloons, or lithotripsy.

We encourage prolonging DCB inflation for at least 30 s, preferably 60 s if well tolerated by the patient.[2] The decision to implant a stent after the SCB is left at the discretion of the operator, but recommended only in case of residual dissection at least type C and in the presence of coronary flow less than TIMI3. We encouraged the Investigators not to stent the other types of minor dissections.[3]

Study end points and clinical follow-up

The purpose of this study is to evaluate SCB performance in terms of efficacy and safety when used for coronary angioplasty in a wide spectrum of coronary artery disease, in a real-world population.

Primary study endpoint is clinically indicated target-lesion revascularization (TLR) at 12 months (any TLR following recurrences of symptoms, either stable or unstable). Secondary endpoints are angiographic success, defined as residual stenosis less than 50% and TIMI3 coronary flow; procedural success, defined as angiographic success and absence of adverse cardiovascular events during hospitalization; major adverse cardiac events (MACE), a composite endpoint of cardiac death, acute myocardial infarction (MI) and need for TLR at 6, 12, 24 and 36 months of implantation; every single element determining the MACE endpoint up to 36 months of follow-up.

After the procedure, all patients are clinically evaluated (with visit or phone call) at 1, 6, 24 and 36 months. After 12 months an office visit is required per protocol. Angiographic follow-up is not recommended unless clinically indicated.

All the demographic and clinical data are collected through an electronic data capture system. This system is compliant with Title 21, Part 11 of the Code of Federal Regulations and with the EU GMP Annex 11 about electronic records for patients.

A quality check for all entered data is performed by a dedicated team of physicians. All clinical adverse events are centrally adjudicated by a blinded committee of physicians who analyze all source documents provided by the centers. A prespecified interim analysis after the enrollment of patients which also had complete 12 months' clinical follow-up was scheduled, aiming at assessing the immediate performance and short-term safety profile of the device.

Statistical analysis

Continuous variables are expressed as mean values ± SD, values are reported as numbers with relative percentages of SD. *P* values less than 0.05 are considered statistically significant. Cumulative event rates have been analyzed using the Kaplan–Meier method, and the rate differences among the groups estimated using the log-rank test. All analyses are performed using the SPSS 21.0 software package (SPSS, Chicago, Illinois, USA). Cox multivariate analysis was performed to assess the independent predictors of the primary endpoint TLR at 1 year, including several variables, which differ at univariate analysis or with significant association with TLR.

Results

By June 2019, out of 5930 patients treated with PCI at the study centers, 712 were screened and finally a total of 642 patients were consecutively treated with a SCB and enrolled in the EASTBOURNE registry. We excluded 70 patients from the enrollment: 52 for unsuccessful predilatation, 14 for severe calcification (judged by the operator) and 4 for other minor reasons.

The overall use of DCB at the study centers was variable between 8 and 34% of PCIs performed during the enrollment phase of the study. The entire cohort had complete 12-month clinical follow-up and entered the interim analysis prespecified in the study protocol. The baseline demographics, lesions characteristics and procedural details of the patients are shown in Table 1. There was a history of diabetes in 263 (41%) patients, and stable coronary artery disease was the clinical presentation in 353 (55%) patients. Differently than in other DCB studies, de-novo lesions represented more than half (55%) of all treated lesions. Notably, predilatation, requested per protocol, was performed in 95% of the cases. Procedural success was obtained in 98.6% of the cases, and in only 7.5% of the cases a DES was implanted after SCB use in bailout. Twenty-eight percent of the patients received a DES in another vessel during index hospitalization.

The clinical outcome at 12 months is shown in Table 2. The primary study endpoint, TLR, occurred in 16 patients (2.5%), whereas total deaths and MACE were, respectively, 6 (0.9%) and 37 (5.8%). MI occurred in 15 (2.3%) patients of the cohort. Bleeding academic research consortium 3–5 bleedings occurred in two (0.3%) of the population. After 12 months 356 patients (55.5%) were still on double antiplatelet therapy, usually because they had an ACS at admission. Figure 2 shows the Kaplan–Meier curves for the occurrence of the primary endpoint of TLR in the overall, ISR and in the native-vessel disease group. TLR occurred in 14 patients (5.4%) in the ISR and 2 (0.5%) in the de-novo lesion setting, with a significantly lower occurrence in the latter group ($P = 0.0008$). Table 3 describes the major determinants of the primary endpoint TLR at 1 year by means of univariate and multivariate analysis.

Table 1 Baseline clinical, angiographic and procedural characteristics

$n = 642$	
Age (years) (mean ± SD)	65.2 ± 11.6
Female, *n* (%)	177 (27.6)
Diabetes mellitus, *n* (%)	263 (41.0)
Hypertension, *n* (%)	597 (74.0)
Multivessel disease, *n* (%)	372 (58.1)
Previous MI, *n* (%)	263 (44.2)
Previous CABG, *n* (%)	76 (12.8)
Previous PCI, *n* (%)	408 (68.4)
Stable CAD, *n* (%)	353 (55.1)
Unstable angina, *n* (%)	111 (17.3)
STEMI, *n* (%)	51 (7.9)
NSTEMI, *n* (%)	128 (20.0)
De-novo lesions, *n* (%)	364 (55.0)
ISR, *n* (%)	278 (45.0)
DES-restenosis, *n*	231
Diameter stenosis pre (% ± SD)	83 ± 14
RVD (mm ± SD)	2.58 ± 0.76
Lesion length (mm ± SD)	18.4 ± 9.0
MLD (mm ± SD)	0.70 ± 0.69
Multivessel PCI, *n* (%)	270 (42)
Lesion predilatation, *n* (%)	610 (95)
Stent use after SCB (DES), *n* (%)	48 (7.5)
Procedural success, *n* (%)	633 (98.6)
Device not deployed, *n* (%)	1 (0.15)
SCB length (mm) (mean ± SD)	22.3 ± 7.6
SCB diameter (mm) (mean ± SD)	2.6 ± 0.6
Inflation pressure (bar) (mean ± SD)	10 ± 4
Inflation time (s) (mean ± SD)	59 ± 21

CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug-eluting stent; ISR, in-stent restenosis; MI, myocardial infarction; MLD, minimal lumen diameter; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RVD, reference vessel disease; SCB, sirolimus-coated balloon; STEMI, ST-segment elevation myocardial infarction.

Table 2 Clinical outcome at 12 months

$n = 642$	
TLR, *n* (%)	16 (2.5)
Death, *n* (%)	6 (0.9)
MI, *n* (%)	15 (2.3)
MACE, *n* (%)	37 (5.8)
On DAPT, *n* (%)	356 (55.5)

BARC, bleeding academic research consortium; DAPT, double antiplatelet therapy; MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target-lesion revascularization.

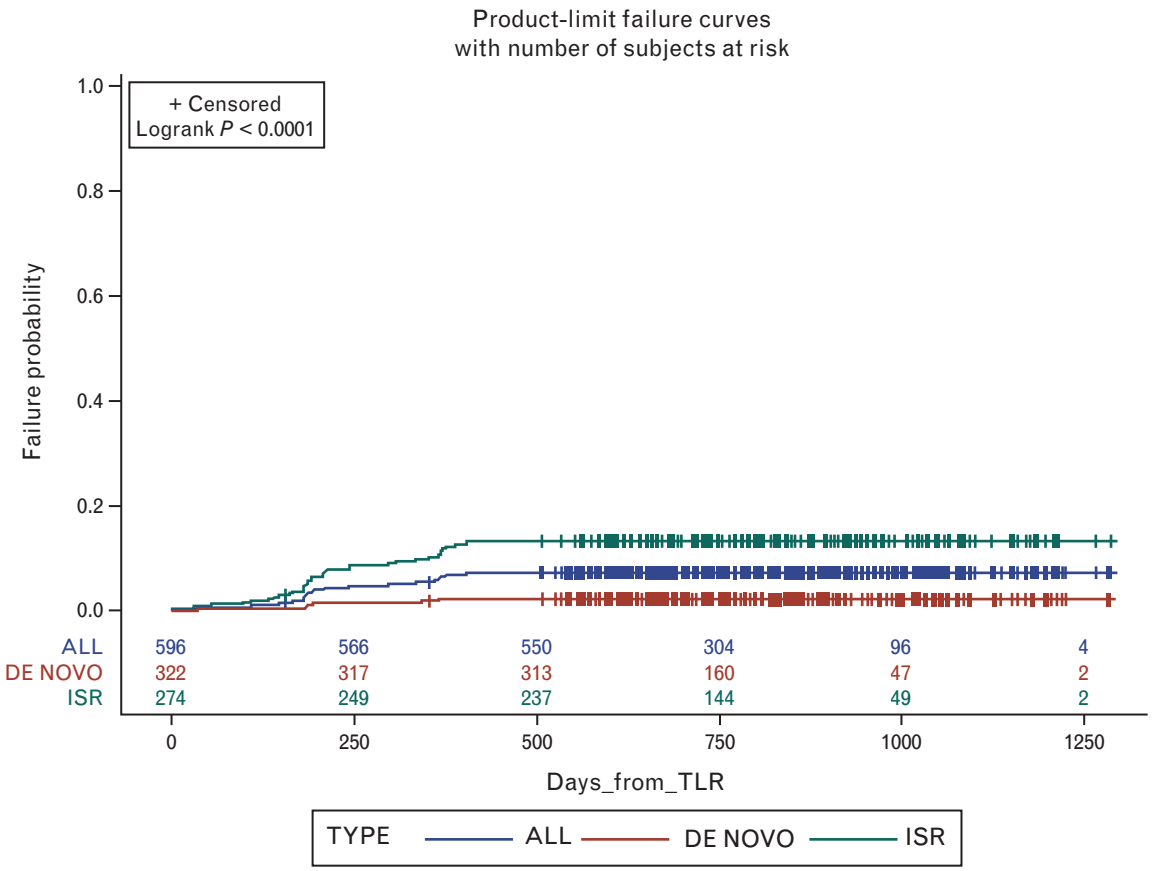
Discussion

The EASTBOURNE registry aims to evaluate the clinical performance of a novel sirolimus-eluting DCB, in a broad population of patients affected by coronary artery disease. Given the novelty of this technology, we decided to perform an interim analysis on the immediate performance and the mid-term clinical outcome of Magic Touch. The results presented here show a safety profile comparable with other paclitaxel-eluting DCB, with no cases of target-lesion thrombotic events within the first 12 months. Indeed, the need for further revascularization as expressed by clinically indicated TLR at mid-term follow-up is low, especially if we consider the high rate of ACS, diabetic patients and overall complexity of the lesions.

Since the first approval of DCB in Europe, all available devices prior to this one eluted paclitaxel, an antiproliferative agent that inhibits the depolymerization of cellular microtubules between metaphase and anaphase, thus, blocking the cell division. The lipophilic nature of paclitaxel renders it particularly appealing for its delivery upon balloon inflation, its diffusion on the treated vessel wall and penetration into the *tunicae media* and *adventitia*, where it is able to exert its effects.[3]

However, the limited therapeutic window and difficulties in finding an adequate drug carrier, along with several other issues, including the high performance of currently available DES, led to a limited diffusion of this technology in the European countries, ranging between 2 and

Fig. 2



Kaplan–Meier curves for the primary endpoint of target-lesion revascularization at 12 months, in the total population, the in-stent restenosis and de-novo cohortes. ISR, in-stent restenosis; TLR, target-lesion revascularization.

15% of the overall number of PCIs. To add some fuel to the topic, recently a meta-analysis showed a higher risk of mortality with paclitaxel-eluting devices when applied for peripheral interventions, at 2 and 4–5 years.[4] Despite this finding being debatable due to the lack of biological plausibility and the presence of serious methodological flaws in the meta-analysis,[5–7] the effect was devastating in the field of peripheral interventions, and led the Federal Drug Administration to issue three warnings on paclitaxel-eluting devices until new data were

Table 3 Univariate and multivariate analysis of the primary endpoint target-lesion revascularization

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
TLR 1 year						
Hypertension	1.18	0.74–1.6	0.3	1.34	0.94–1.2	0.09
Diabetes	1.72	0.88–3.37	0.1	4.11	1.02–16.58	0.047
Creatinine clearance <50 ml/min	1.63	1.17–2.27	0.004	2.33	1.55–3.49	<0.001
LVEF	0.96	0.93–0.99	0.009	0.91	0.84–0.98	0.02
Previous PCI	1.84	0.94–3.57	0.07			
De-novo lesion	1.55	0.98–2.1	0.05			
Lesion length (increase 1 mm)	1.07	1.03–1.12	0.001	1.12	1.02–1.22	0.016
Stent use after SCB (DES), *n* (%)	1.4	0.95–1.3	0.5	1.5	0.93–1.61	0.35
Acute kidney injury	2.8	0.75–10.6	0.1	0.006	0–0.61	0.03
Procedural success	0.29	0.1–0.85	0.03	0.32	0.002–0.53	0.04
Oral anticoagulation	2.6	1.01–6.83	0.04			

DES, drug-eluting stent; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SCB, sirolimus-coated balloon; TLR, target-lesion revascularization.

provided. Recently, an aggregate-data meta-analysis seemed to show no relation between paclitaxel application in the coronary arteries and late mortality.[8]

This matter and some recollections of the previous application of paclitaxel to coronary DES (namely, Taxus stent; Boston Scientific, Marlborough, Massachusetts, USA) render sirolimus particularly appealing for both coronary and peripheral local applications. Sirolimus is a cytostatic, immunosuppressive and antiproliferative drug which inhibits mTOR, a protein chinase, with resulting immunosuppressive effect. The reduced lipophilia of sirolimus has been overcome in this specific device thanks to a specific technology named Nanoluté, which aims at creating submicron spheres of sirolimus, protected by a phospholipid bilayer, which favors drug transit from the balloon surface toward the vessel wall, and helps its penetration and persistence. A calcium-phosphorus component acts by maintaining such spheres adherent and attached to the vessel wall just after balloon inflation.[1]

To this day, we have limited evidence on the performance of SCB for coronary use. In the Indian Nanoluté registry, 332 patients treated with SCB had a rate of TLR of 3.6% after 12 months with no occurrence of thrombotic events.[9] However, in this sponsored registry the events were not centrally adjudicated and a quality check for data entry was not available.[10] The first European experience with an SCB was analyzed in a small prospective, single-center registry: the FASICO study. The first 34 lesions treated with an SCB in a broad and complex population of patients (one-third of the patients had ISR with already failed paclitaxel-DCB PCI) showed an adequate clinical follow-up at 6 months with three cases of TLR and no thrombotic events (all events were centrally adjudicated by a cardiac visit).[11] The FASICO NATIVES registry was a prospective registry of 27 patients with native coronary vessel disease (mean reference vessel diameter was 2.32 ± 0.44 mm). Six-month angiographic follow-up in this cohort of patients showed an LLL of 0.09 ± 0.34 mm, with about one-third of the patients showing an improvement in lumen dimensions during angiographic follow-up (centralized core lab, Cardialysis, Rotterdam, The Netherlands).[12]

The current findings of the EASTBOURNE registry seem to confirm these preliminary data. The high prevalence of diabetes (41%) and previous coronary revascularizations (74% including PCI and coronary artery bypass), and the inclusion of 45% of patients with acute coronary syndrome show a real-world population, at a higher risk if compared with other similar registries on DCB. So far, the largest study available on DCB is the Sequent Please World Wide Registry, a prospective registry which included patients treated with Sequent Please DCB (B. Braun, Melsungen, Germany).[13] In this study, the percentages of diabetes (34%) and acute coronary syndrome (20%) were lower than in our study. Also lesion length (15–17 mm) and the proportion of patients affected by native-vessel disease (23%) instead of ISR were lower than in EASTBOURNE (50%), probably reflecting the different scenario of DCB use in 2019.

In our registry, a high proportion of patients underwent ad-hoc multivessel PCI (44%), either with DES or another DCB. Interesting, in about 10% of the overall population, the culprit lesion was treated using a synergistic approach of DES + SCB, especially in case of long lesions that the operator decided not to treat with multiple or very long stents. A special mention should be made of the low percentage of patients undergoing bailout stenting (7.5%), who were analyzed with the rest of the population: this low reported number may be reflected either by the selection of the participating centers according to their expertise in DCB use, or by the fact that if patients did not receive an 'effective' lesion preparation, they should not have been enrolled, therefore limiting the number of stents used after lesion preparation. Being that this was a device-oriented clinical registry, to obtain a precise assessment of the safety and efficacy of this device, we decided not to include those patients who did not receive the therapy.

In this study, the primary endpoint TLR at 1 year in the ISR cohort (5.4%) was lower than in other studies, where it is usually attested at between 9 and 15% (Fig. 2), but still significantly higher than in the de-novo population. This preliminary information is not new to DCB, considering that some recent paclitaxel-DCB studies showed an increase in the TLR rate for the DES-ISR indication, with lower angiographic and clinical performance if compared with latest-generation DESs.[14,15] We will deeply analyze this information in the final enrolled population with longer follow-up and adequate statistical analysis.

Finally, a few words regarding the mid-term clinical outcome warrant mention. The overall low events encountered at 12 months, all adjudicated by a predefined scientific committee evaluating all source documents, therefore, confirm the good safety and efficacy profile already depicted by the other experiences mentioned earlier. However, a final opinion cannot be drawn until all the patients expected to be enrolled (2000) will have 12 months of clinical follow-up available. We also believe that the extension of the follow-up to 3 years will shed light on the long-term performance of this device. This limitation, in terms of lack of a complete population, is in our opinion justified given the total novelty of the drug and technology, thus we felt it important to publish such preliminary results, to avoid the mistakes that have been made previously with other brands of DCB. Another limitation of the current report is related to the fact that the decision to use an SCB instead of another device was left at the operators' discretion, depending on his/her own

feeling and on device availability. A potential limitation also derives from the fact that these results may not be reproducible in other centers without the certified experience required to participate in EASTBOURNE.

Conclusion

The EASTBOURNE registry is the first and largest study on the use of SCB in humans. The preliminary mid-term follow-up here reported shows a good performance of this device, along with an adequate safety profile.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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