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CORONARY

Sirolimus-Coated Balloon in an All-Comer Population of Coronary Artery Disease Patients

The EASTBOURNE Prospective Registry

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ABSTRACT

BACKGROUND Drug-coated balloons (DCB) represent 1 of the most promising innovations in interventional cardiology and may represent a valid alternative to drug-eluting stents. Currently, some sirolimus-coated balloons (SCB) are being investigated for several coronary artery disease applications.

OBJECTIVES This study sought to understand the role of a novel SCB for the treatment of coronary artery disease.

METHODS EASTBOURNE (All-Comers Sirolimus-Coated Balloon European Registry) is a prospective, multicenter, investigator-driven clinical study that enrolled real-world patients treated with SCB. Primary endpoint was target lesion revascularization (TLR) at 12 months. Secondary endpoints were procedural success, myocardial infarction (MI), all-cause death, and major adverse clinical events (a composite of death, MI, and TLR). All adverse events were censored and adjudicated by an independent clinical events committee.

RESULTS A total population of 2,123 patients (2,440 lesions) was enrolled at 38 study centers in Europe and Asia. The average age was 66.6 ± 11.3 years, and diabetic patients were 41.5%. De novo lesions (small vessels) were 56%, in-stent restenosis (ISR) 44%, and bailout stenting occurred in 7.7% of the patients. After 12 months, TLR occurred in 5.9% of the lesions, major adverse clinical events in 9.9%, and spontaneous MI in 2.4% of the patients. The rates of cardiac/all-cause death were 1.5% and 2.5%, respectively. The primary outcome occurred more frequently in the ISR cohort (10.5% vs 2.0%; risk ratio: 1.90; 95% CI: 1.13-3.19). After multivariate Cox regression model, the main determinant for occurrence of the primary endpoint was ISR (OR: 5.5; 95% CI: 3.382-8.881).

CONCLUSIONS EASTBOURNE, the largest DCB study in the coronary field, shows the safety and efficacy of a novel SCB in a broad population of coronary artery disease including small vessels and ISR patients at mid-term follow-up. (The All-Comers Sirolimus-Coated Balloon European Registry [EASTBOURNE]; NCT03085823)
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The current gold standard treatment strategy for coronary artery disease (CAD) patients consists of the implantation of drug-eluting stents (DES). Recent technological improvements also account for new therapeutic options, including drug-coated balloons (DCB). Since their first clinical application, DCB eluted paclitaxel as an antirestenotic drug, and were mainly used for the treatment of in-stent restenosis (ISR), as an alternative to new prosthesis implantation. Later, DCB have been used for the treatment of some native CAD settings. More recently, newer antirestenotic and antiproliferative drugs, including sirolimus, have been developed and tested, aimed at reducing the mid- and long-term events invariably associated with DES failure. After some interesting preliminary results in pilot studies or small registries,[1-4] the performance of a novel sirolimus-coated balloon (SCB) in a broad spectrum of CAD patients has been tested in a properly sized and all-comer prospective study.

METHODS

STUDY CHARACTERISTICS AND PROCEDURE. The aim of EASTBOURNE (All-Comers Sirolimus-Coated Balloon European Registry; NCT03085823) registry is to observe and evaluate the performance of the MagicTouch (Concept Medical) SCB for the treatment of any type of coronary lesions, including native CAD and ISR. This study is a prospective, multicenter, investigator-driven clinical registry that enrolled a real-world CAD population at 38 centers located in several European and Asiatic countries. Each investigator involved in the study had to certify an adequate experience in DCB percutaneous coronary intervention (PCI), namely the use of at least 30 DCB per year in the last 5 years.

All patients will be followed up to 3 years from their index procedure. A dedicated committee validated the quality of data input in the eCRF, and all events and study endpoints are adjudicated by an independent centralized clinical event committee, which had access to source documents.

Inclusion criteria were quite broad and included all clinical indications for PCI with SCB, following the judgement of the investigator. Exclusion criteria were: 1) patients with known (and untreatable) hypersensitivity or contraindication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, sirolimus, or contrast media; and 2) target lesion/vessel with any 1 of the following characteristics: (a) unsuccessful predilatation of the target lesion, with persisting residual stenosis higher than 50%; (b) severe calcification of the target vessel, either at the lesion site or proximal to the lesion; (c) highly tortuous culprit vessels; and (d) visible thrombus at the lesion site, not treatable with manual aspiration. Left main stem disease and ST-segment elevation myocardial infarction (MI) did not constitute an exclusion criterion.

The decision whether to use the DCB or any other treatment strategy was left to the operator's decision. PCI was performed according to international consensus documents.[5,6] Lesion preparation was mandatory with any type of device deemed necessary by the operator, and bailout stenting was discouraged unless DCB PCI hesitated into a flow-limiting dissection (TIMI flow grade <3) or acute vessel recoil after a minimum of 5 minutes from drug application. In case of stenting, DES implantation was recommended. The antithrombotic regimen was left to the operator's choice, but a minimum of 30-day dual antiplatelet

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
CAD = coronary artery disease
DAPT = dual antiplatelet therapy
DCB = drug-coated balloon(s)
DES = drug-eluting stent(s)
ISR = in-stent restenosis
MACE = major adverse cardiovascular event(s)
MI = myocardial infarction
PCB = paclitaxel-coated balloon
PCI = percutaneous coronary intervention
SCB = sirolimus-coated balloon(s)
TLF = target lesion failure
TLR = target lesion revascularization

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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therapy (DAPT) was suggested in case of stable coronary disease. In case of acute coronary syndrome (ACS) or bailout stenting, a regimen of 6 to 12 months was indicated. The study received the approval of the central ethical committee of the coordinating center (ASST FBF-Sacco, Milano: Comitato Etico Area B Milano, Italy), and thereafter from the ethical committees of all participating centers.

FOLLOW-UP. All patients were followed up clinically, with planned visits at 6 and 12 months from the index procedure. A phone call from the investigators is planned at 24 and 36 months, and at final study follow-up. Angiographic surveillance or stress tests were not required by the protocol but were dictated by clinical reasons only.

STUDY DEVICE. The MagicTouch sirolimus DCB has been previously described.[7] Briefly, sirolimus (whose dosage per mm^2 of balloon surface is 1.27 mg/mm^2) is eluted, thanks to a dedicated nanocarrier technology, the drug being encapsulated in a phospholipid bilayer working as a drug carrier. Available lengths range from 10 to 40 mm and diameters from 1.50 to 4.00 mm. The delivery system is a semicompliant coronary balloon with a low tip profile and a hydrophilic coated surface, activated upon contact with blood. Recommended inflation time is 60 seconds, with a minimum of 30 seconds. A balloon length exceeding the lesion at least 3 mm proximally and distally was recommended. If needed, multiple SCB were allowed.

OUTCOME MEASURES. The study primary endpoint was clinically indicated target lesion revascularization (TLR) at 12 months, defined as reintervention of the target lesion after demonstration of at least 70% narrowing and the presence of objective evidence of ischemia by stress test or functional assessment. Secondary endpoints were procedural success, a compound of angiographic success without in-hospital complications; MI during follow-up; cardiac death during follow-up; major adverse cardiovascular events (MACE), a composite of TLR, MI, and cardiac death, during follow-up. Angiographic success was defined as TIMI flow grade 3 with percent diameter stenosis <30%. Patients have been followed by hospital visits at 12 months and will undergo 24- and 36-month follow-up by phone interview. Angiographic follow-up was not requested unless clinically indicated. Furthermore, definite/probable vessel thrombosis was defined according to the Academic Research Consortium criteria.

STATISTICAL ANALYSIS. Patient characteristics are summarized using descriptive statistics. Mean ± SD and median (IQR) were used for continuous variables with normal and non-normal distribution, respectively. Absolute frequency (percentage) was used for categorical variables. Continuous variables were compared between de novo and ISR groups using the *t*-test and Mann-Whitney *U* test, whereas the chi-square test or Fisher exact test was used for categorical variables (when some of the cells have counts fewer than 5).

The relationship between TLR and lesion subset (ISR or de novo) was estimated through the Kaplan-Meier curves method (and tested by log-rank test).

The multivariate Cox regression model was used to assess the association between lesion subset and the TLR outcome within 12 months. The model was adjusted for potential confounding factors, such as: patient age, diabetes mellitus, hypercholesterolemia, arterial hypertension, congestive heart failure, previous myocardial infarction, multivessel disease, multivessel PCI, and lesion length. Ten percent statistically significant parameters in univariate analysis ($P < 0.10$) were analyzed in multivariate analysis. Multicollinearity was assessed using variance inflation factor, which resulted for all coefficients <1.2. The choice of the variables analyzed in the model followed a statistical criterion in primis, followed by a clinical one, aiming at choosing those relevant for the study outcome.

All tests were 2-tailed, and a *P* value <0.05 was considered significant. All statistical analyses were performed using R version 4.0.1 (R Foundation for Statistical Computing).

RESULTS

Between September 2016 and November 2020, a total of 2,123 patients with 2,440 lesions have been enrolled in the European and Asiatic study centers. The experience of the centers in DCB PCI was variable, with DCB use ranging between 8% to 54% of the interventions performed each year by the operators.

Baseline characteristics are reported in **Table 1**. The average age was 66.6 ± 11.3 years, and 41.5% of patients had diabetes. Multivessel CAD was present in 59.3% of the patients, a previous MI in 42.9%, and a previous PCI in 66.3%; ACS was the clinical indication for PCI in 46.6%, depicting a real-world patient population. De novo lesions, mostly in small coronary vessels, were treated in 1,173 patients (56%), and ISR in 910 (44%): the clinical characteristics of these 2 patient populations were significantly different (**Table 1**).

TABLE 1 Patient Population and Lesion Characteristics

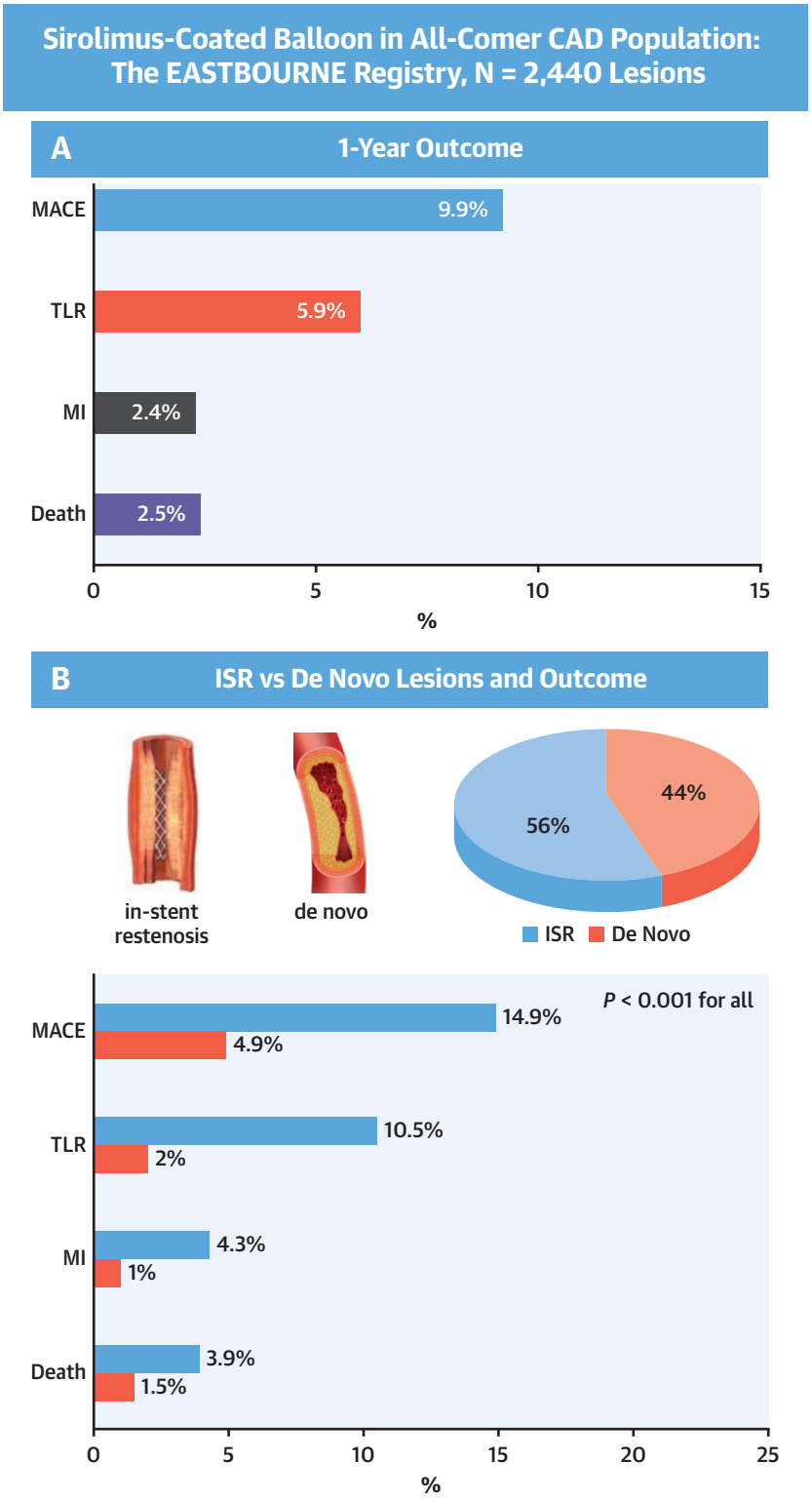
Study Population	Entire Population (N = 2,083)	Patients With De Novo Lesions (n =1,173)	Patients With ISR (n = 910)	*P* Value
Age, y	66.6 ± 11.3	64.7 ± 11.8	69.1 ± 10.0	<0.001
Female	393 (18.9)	216 (18.4)	177 (19.5)	0.587
Arterial hypertension	1,604 (77.0)	840 (71.6)	764 (84.0)	<0.001
Diabetes mellitus	864 (41.5)	452 (38.5)	412 (45.3)	0.002
Insulin-dependent diabetes mellitus	283 (13.6)	120 (10.2)	163 (17.9)	<0.001
Dyslipidemia	1,496 (71.8)	786 (67.0)	710 (78.0)	<0.001
Congestive heart failure	170 (8.2)	76 (6.5)	94 (10.3)	0.002
Multivessel disease	1,235 (59.3)	631 (53.8)	604 (66.4)	<0.001
LV ejection fraction, %	51.7 ± 11.0	52.3 ± 11.5	51.1 ± 10.4	0.019
Previous MI	894 (42.9)	361 (30.8)	533 (58.6)	<0.001
Previous PCI	1,380 (66.3)	503 (42.9)	877 (96.4)	<0.001
Previous CABG	244 (11.7)	81 (6.9)	163 (17.9)	<0.001
Indication for PCI				
NSTEMI	445 (21.4)	257 (21.9)	188 (20.7)	<0.001
STEMI	159 (7.7)	127 (10.8)	32 (3.5)	
Unstable angina	364 (17.5)	156 (13.3)	208 (22.9)	
Stable CAD	1,115 (53.5)	633 (54.0)	482 (52.9)	
Lesion Characteristics	**All Lesions (N = 2,339)**	**(n = 1,284)**	**(n = 1,055)**	
RVD	2.62 ± 0.58	2.34 ± 0.43	2.97 ± 0.56	<0.001
Lesion length	18.76 ± 9.14	19.55 ± 9.60	17.81 ± 8.46	<0.001
MLD	0.82 ± 0.97	0.76 ± 0.92	0.88 ± 1.02	0.007
Calcification pattern, %				
Mild/none	47.0	35.1	67.4	0.003
Moderate	46.2	56.8	27.9	
Severe	6.8	8.1	4.7	
Lesion predilatation	2142 (91.6)	1141 (88.9)	1001 (94.9)	<0.001
Diameter balloon predilation, mm	2.5 (2.0-3.0)	2.0 (2.0-2.5)	3.0 (2.5-3.5)	<0.001
Procedural complications	40 (1.7)	22 (1.7)	18 (1.7)	>0.999
Stent implantation after DCB	181 (7.7)	112 (8.7)	69 (6.5)	0.059
Procedural success	2,284 (97.6)	1,242 (96.7)	1,042 (98.8)	0.002

Values are mean ± SD, n (%), or median (IQR).

CABG = coronary artery bypass graft intervention; CAD = coronary artery disease; DCB = drug-coated balloon; ISR = in-stent restenosis; LV = left ventricular; MI = myocardial infarction; MLD = minimal lumen diameter; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; STEMI = ST-segment elevation myocardial infarction.

Table 1 also describes the procedural characteristics of the enrolled population. Notably, reference vessel diameter was 2.62 ± 0.58 mm, and lesion length 18.76 ± 9.14 mm. Lesion preparation occurred in 91.6% of the lesions, slightly more in the ISR patients (94.9% vs 88.9%; $P < 0.001$). Forty-two percent of patients underwent multivessel PCI during index PCI. Device malfunction occurred in 5 cases (0.2%) and procedural complications in 40 lesions (1.7%). Of the 40 procedural complications, 29 were periprocedural MI, and 3 vessel perforations were managed during the intervention. We did not observe any acute or subacute vessel closure. Notably, procedural characteristics also were significantly different between patients undergone de novo vs ISR angioplasty (Table 1). The necessity to stent the lesion due to flow-limiting dissection or acute vessel recoil occurred in 181 lesions (7.7%: 8.7% in de novo, 6.5% in ISR lesions). Procedural success occurred in 97.6% of the lesions.

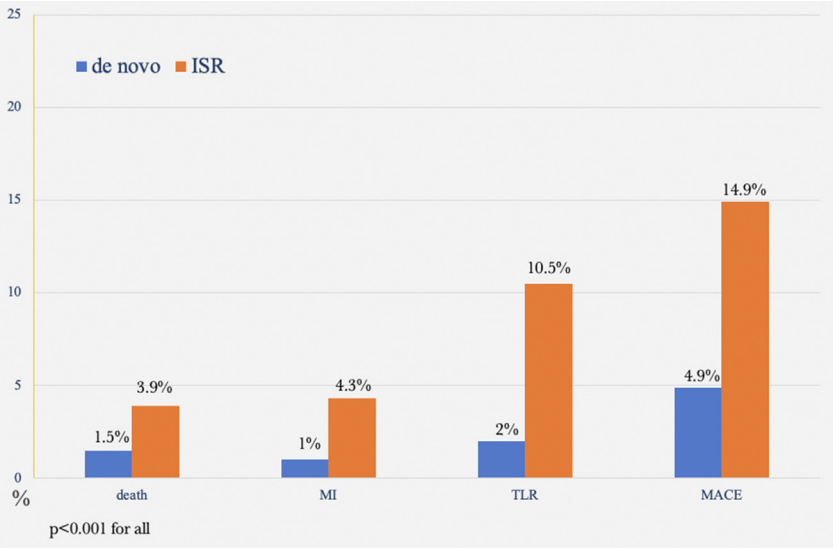
CENTRAL ILLUSTRATION Registry Overview and Findings



Cortese B, et al. J Am Coll Cardiol Intv. 2023;16(14):1794–1803.

CAD = coronary artery disease; EASTBOURNE = All-Comers Sirolimus-Coated Balloon European Registry; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; TLR = target lesion revascularization.

FIGURE 1 Clinical Outcome at 1 Year in the De Novo and ISR Populations



ISR = in-stent restenosis; TLR = target lesion revascularization.

One-year follow-up (median IQR: 363 days) (**Central Illustration**) was available for 1,927 of the patients (92.5%) and is reported in **Figure 1**. At 1 year, 34% of the patients were still on DAPT. TLR occurred in 127 lesions (5.9%) and was more frequent for patients with ISR vs native vessel disease (10.5% vs 2.0%; risk ratio: 1.90; 95% CI: 1.13-3.19; $P < 0.001$). **Figure 2** describes the Kaplan-Meier curve for the occurrence of the primary endpoint TLR in these 2 populations. The all-cause death rate was 2.5%, cardiac death 1.5%, MI 2.4%, and BARC (Bleeding Academic Research Consortium) type 3 or 5 bleedings 0.7%. MACE occurred in 9.9% of the patients (4.9% in the de novo group, and 14.9% in the ISR one; $P < 0.001$) (**Figure 1**). **Figure 3** describes the clinical outcome in the diabetic population vs the nondiabetic one.

Table 2 describes multivariate Cox regression model results, ISR and reference vessel diameter being the major determinants for the occurrence of the primary endpoint TLR within 12 months.

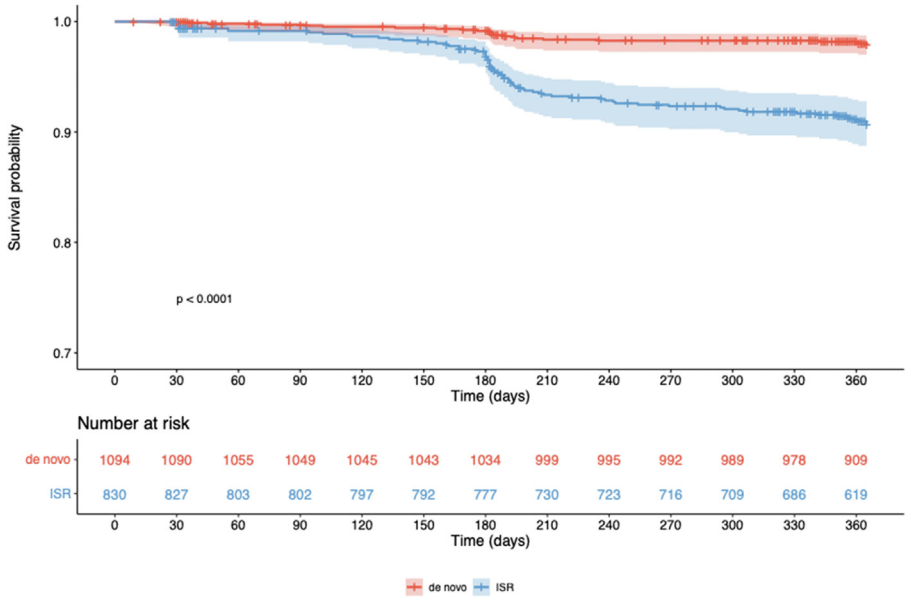
DISCUSSION

SUMMARY OF THE STUDY RESULTS. The results of this investigator-driven study that enrolled >2,100 all-comer patients, the largest in the coronary field, can be summarized as follows:

1. SCB is a safe device for a broad spectrum of patients affected by CAD/lesions;
2. SCB is more effective for de novo small vessels vs ISR lesions, similarly to other previous treatment strategies (**Figure 2**).

ADVANTAGES OF DCB ANGIOPLASTY. Differently from DES, DCB are characterized by the absence of permanent prosthesis and polymer, thus their impact on vessel geometry and structure is mild. On the other hand, DES have a better immediate angiographic outcome, but are associated with a continuous, although low, yearly increase in adverse events, which can reach the not negligible rate of 43.8% in terms of target lesion failure (TLF) after 10 years,[8] with a yearly trend of 3.3% events after the first year. In case of more complex lesion subsets, such as small vessel disease or long lesions, the risk of DES failure with currently available devices is usually higher, leading to an almost double increase in TLF.[9,10] Moreover, real-life patients share a bleeding and thrombotic risk that is higher than the one observed in patients usually included in randomized controlled trials. In this panorama, a DCB strategy may be an alternative to metallic platforms, due to the high safety and efficacy profile.[11]

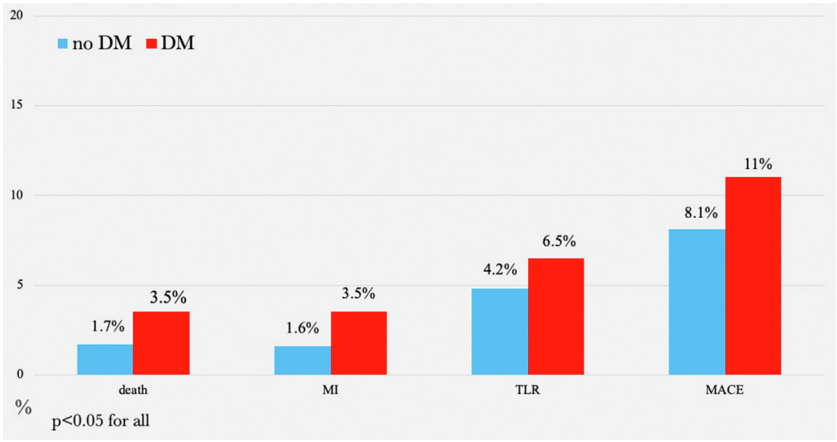
FIGURE 2 Kaplan-Meier Curves of the Primary Endpoint of TLR



Kaplan-Meier curves of the primary endpoint of TLR according to initial lesion setting (de novo lesion or ISR). Abbreviations as in Figure 1.

PREVIOUS STUDIES. Previously, only 1 large multicenter, prospective registry described the clinical profile of a paclitaxel-coated balloon (PCB) in a broad spectrum of CAD patients.[12] The SeQuent world-wide registry included 2,095 patients, showing a 9-month rate of TLR in 5.2% and cardiac death in 1.8% of patients, findings similar to the ones shown in EASTBOURNE after 12 months. However, there are some differences between these 2 registries that should be underlined. First of all, in EASTBOURNE, a higher number of de novo lesions were enrolled (56% vs 27%), probably reflecting the change in the panorama of treatment of CAD 10 years later. Moreover, in case of ISR, only DES ISR were included

FIGURE 3 Clinical Outcome at 1 Year, According to Initial Diabetic Status of the Patients



DM = diabetes mellitus; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; TLR = target lesion revascularization.

TABLE 2 Multivariate Cox Regression Model Results

	HR	95% CI	*P* Value
ISR	1.465	0.945 to 1.984	<0.001
Patient age, y	−0.019	−0.039 to 0.001	0.065
Diabetes mellitus	0.277	−0.137 to 0.690	0.190
Hypercholesterolemia	−0.297	−0.772 to 0.178	0.221
Arterial hypertension	0.277	−0.294 to 0.847	0.342
Congestive heart failure	0.166	−0.479 to 0.812	0.613
Previous myocardial infarction	0.198	−0.234 to 0.629	0.369
MVD	0.546	0.050 to 1.041	0.031
Multivessel PCI	−0.186	−0.622 to 0.250	0.403
Lesion length, mm	−0.003	−0.027 to 0.020	0.775

MVD = multivessel disease; other abbreviations as in Table 1.

in EASTBOURNE, whereas in the SeQuent Please registry, 62% of the cases of restenosis were bare-metal stent restenosis, a usually more benign entity associated with better outcome after treatment. However, the most important difference among these 2 studies pertains to the drug eluted, sirolimus instead of paclitaxel. PCB have shown an adequate safety and efficacy profile in several patient and lesion settings. The DAEDALUS (Difference in Anti-restenotic Effectiveness of Drug-Eluting Stent and Drug-Coated Balloon Angioplasty for the Occurrence of Coronary In-Stent Restenosis) study showed a moderate increase in the efficacy of DES vs PCB in the ISR setting in terms of 3-year TLR (12% vs 16%; HR: 1.32; 95% CI: 1.02-1.70).[13] On the other hand, the BASKET-SMALL II (Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions II) study showed no differences in terms of 3-year MACE between PCB and DES in the de novo lesion setting (15% in both groups; HR: 0.99, 95% CI: 0.68-1.45).[14]

This SCB has been tested previously in small registries[1-3,15] and 2 randomized controlled trials are currently comparing it to a PCB and a DES in the de novo lesion setting. TRANSFORM I (Treatment of Small Coronary Vessels: MagicTouch Sirolimus Coated Balloon) is a mechanistic study which randomized 120 patients to SeQuent Please (B. Braun) and MagicTouch after lesion assessment with optical coherence tomography, evaluating net lumen gain during 6 months' angiographic follow-up.[16] TRANSFORM II (Sirolimus-Coated Balloon Versus Drug-Eluting Stent in Native Coronary Vessels) is randomizing patients to everolimus-eluting stents and MagicTouch, and will evaluate the rate of TLF at 1 year (primary endpoint) and subsequently through the 5-year follow-up.[17] In the meanwhile, the current registry has provided valuable insights into the potential role of SCB in a broad spectrum of patients without raising safety issues and providing a reassuring efficacy profile, mostly in the de novo setting, where we encountered a TLR rate of 2%, despite the relatively low predilatation rate (89% in this cohort).

IS ISR THE ACHILLES' HEEL OF DCB ANGIOPLASTY?

On the other hand, in the ISR setting, the rate of TLR (10.5%) was found higher and similar to the one already observed with other DCB,[13] despite the absence of safety warning signals. The reasons for this lower efficacy might be attributed to an inadequate understanding of the reasons for ISR (intravascular imaging was used in only 10% of ISR cases) and a low implementation of modern lesion preparation devices (noncompliant or scoring balloons, intravascular lithotripsy, all below 10% of the cases). The long-term follow-up in this setting, and other ongoing studies (a investigational device exemption Food and Drug Administration study is currently being settled up), will shed light on the real value of this DCB in the ISR setting.

DAPT REGIMEN WITH DCB. Another potential advantage of DCB is related to the potentially shorter DAPT regimen in case of patients at high bleeding risk. In EASTBOURNE, we implemented a 1-month DAPT regimen in case of stable CAD and 6 to 12 months in case of ACS, according to the current guidelines. Unfortunately, no evidence is available on the correct duration of DAPT after solo-DCB angioplasty yet. Bleedings BARC type 3 to 5 in the whole population of this registry were relatively few, occurring in 0.6% of the population, but further analyses and direct comparison with DAPT regimen in DES patients are needed.

STUDY LIMITATIONS. First of all, it is a single-arm, thus open-label, registry with all the inherent limitations; however, all outcomes were adjudicated by an independent clinical events committee based on prespecified criteria after revision of source documents, thus in part reducing this concern. Another limitation is that the decision to use an SCB instead of another device was left at the operators' discretion, depending on his/her own feeling or the availability of the device. A core laboratory for angiographic examinations was not available for qualitative comparative analysis. The results depicted in the de novo cohort of patients cannot be generalized to the whole lesion setting, because this finding in EASTBOURNE is related to small coronary vessels. Another limitation of the current study is that despite it being strongly

suggested in the protocol, only 91.6% of the lesions received a preparation before DCB use, a habit that cannot be recommended. Consequently, because approximately 20% of patients did not undergo DCB PCI due to flow-limiting dissection or percent stenosis >50%, we have to acknowledge that not all patients in a real-world setting can undergo a DCB PCI. Finally, all centers have been selected according to the experience of the investigators, thus the reproducibility of these results in centers without experience in DCB has to be investigated further.

CONCLUSIONS

The EASTBOURNE investigator-driven registry shows an encouraging safety and efficacy profile of a novel sirolimus-coated balloon at mid-term follow-up, in a broad spectrum of CAD patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The study was an independent, investigator-driven study which received fundings by Envision Scientific. This society had no role in the protocol definition, selection of centers, conduction of the study and interpretation of the results. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Drug-coated balloons are increasingly used in several lesions and patients' settings, with sirolimus having been recently added as an alternative to the well-studied paclitaxel.

WHAT IS NEW? The EASTBOURNE prospective investigator-driven international registry enrolled a broad number of coronary artery disease patients showing the safety and efficacy of the MagicTouch sirolimus-coated balloon.

WHAT IS NEXT? It is now mandatory to confirm these findings with adequately powered studies comparing the performance of sirolimus-coated balloons with current era drug-eluting stents in a randomized fashion.

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