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Two-year outcomes of sirolimus-coated balloon angioplasty for coronary artery disease: the EASTBOURNE Registry

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Despite multiple refinements in drug-eluting stent (DES) technology and implantation techniques, percutaneous coronary intervention (PCI) with DES is complicated by the continuous accrual of clinical events due to thrombosis and in-stent restenosis (ISR). Drug-coated balloon (DCB) angioplasty offers advantages related to drug elution from the balloon surface and the absence of permanent struts, and it yields non-inferior clinical outcomes in patients with ISR and *de novo* small vessel disease[1]. Historically eluting paclitaxel, DCBs with newer antiproliferative drugs, including sirolimus, have been developed and tested for DCB PCI[2,3]. To date, large-scale evidence on safety and efficacy beyond 1 year after sirolimus-coated balloon (SCB) PCI is limited.

EASTBOURNE (ClinicalTrials.gov: NCT03085823) is a prospective, multicentre, investigator-driven cohort study evaluating the performance of the MagicTouch SCB (Concept Medical) for PCI in all-comer patients enrolled at 38 European and Asian centres between September 2016 and November 2020. The study design and 1-year results have been previously reported[3]. Briefly, real-world patients with any clinical indication for PCI with DCB, i.e., *de novo* small vessel disease and ISR, were included. Among the exclusion criteria were (i) unsuccessful predilation of the target lesion with persisting residual stenosis higher than 50%, (ii) severe calcification of the target vessel (at the lesion site or proximal to it), (iii) a highly tortuous target vessel and (iv) visible thrombus at the lesion site, not treatable with manual aspiration **(Supplementary Appendix 1)**. The 2-year primary endpoint assessment consisted of clinically indicated target lesion revascularisation (TLR), defined as reintervention of the target lesion after demonstrating at least 70% narrowing and the presence of objective evidence of ischaemia by stress test or functional assessment.

The baseline characteristics of included patients have been published previously **(Supplementary Table 1)**. Compared to patients with ISR, those treated for *de novo* disease were less often diabetic (38% vs 45%; p=0.002), had smaller reference vessel diameters (2.3 mm vs 3.0 mm; p<0.001), underwent predilation less often (89% vs 95%; p<0.001) and tended to have stents implanted more often (9% vs 6%; p=0.059).

Among 2,123 patients, 2-year clinical follow-up was available for 90% (n=1,907) of patients. The cumulative incidence of the primary endpoint, clinically indicated TLR, was 7% (n=163) at 2-year follow-up, with 36 events (1%) accruing between the 1- and 2-year follow-up **(Central illustration)**. Between years 1 and 2, the incidence of major adverse cardiac events (MACE; a composite of cardiac death, spontaneous myocardial infarction [MI] and TLR) increased by 1.3% to 11.2% (n=234), cardiac death by 0.1% to 1.6% (n=34) and spontaneous MI by 1.7% to 4.1% (n=86). Death from any cause was observed in 5.3% (n=111) of cases, TVR in 6.8% (n=141) and Bleeding Academic Research Consortium (BARC) 2-5 bleeding in 1.3% (n=28). The incidence of TLR was lower in patients with *de novo* lesions than in those with ISR (2.6% vs 12.3%; p<0.001); this was confirmed in the time-to-event analysis, including a landmark analysis at 1-year follow-up ($p_{log\text{-}rank}$<0.001 for all comparisons) **(Supplementary Figure 1)**. Similarly, compared to patients with ISR, those with *de novo* lesions experienced less MACE (5.5% vs 18.6%; p<0.001), death (3.5% vs 7.7%; p<0.001), cardiac death (0.6% vs 3.0%; p<0.001), spontaneous MI (2.6% vs 6.1%; p<0.001)

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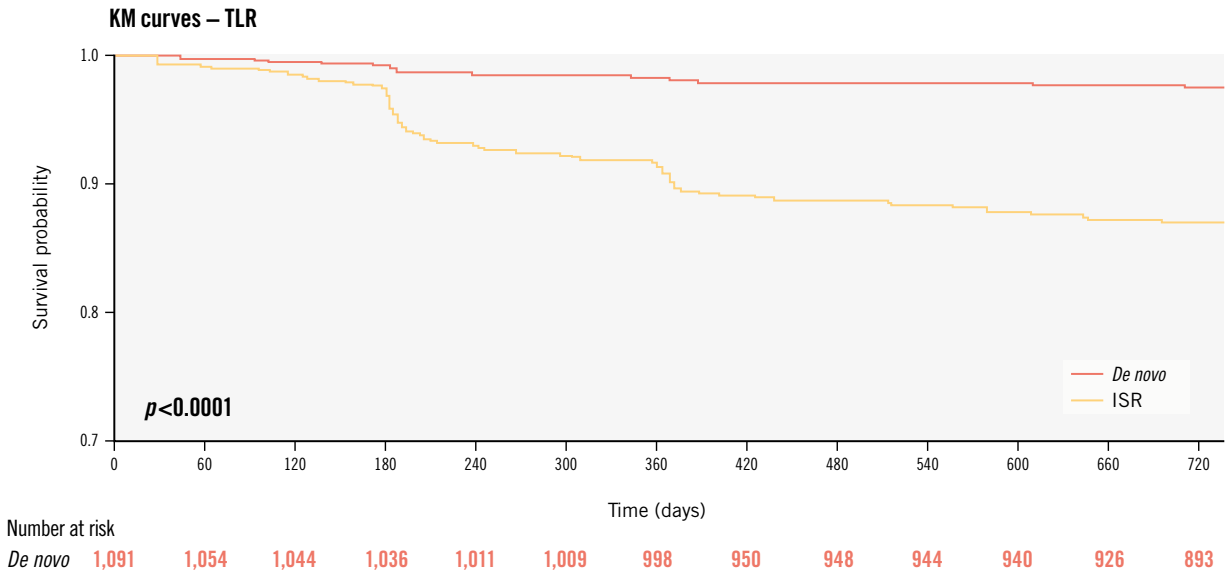
Kaplan-Meier estimates of the primary endpoint up to 2-year follow-up according to the type of lesion treated.



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ISR: in-stent restenosis; KM: Kaplan-Meier; TLR: target lesion revascularisation

and TVR (2.6% vs 12.2%; p<0.001). No difference in BARC 2-5 bleeding was found between the groups (0.9% vs 1.7%; p=0.153). After multivariable adjustment, the risk for undergoing clinically indicated TLR at the 24-month follow-up was higher in patients with ISR, females, patients with smaller visually estimated minimal lumen diameters, and those with larger SCB diameters, and when more than one lesion was treated during the index procedure **(Supplementary Table 2)**.

The main findings of our study assessing 2-year follow-up outcomes of patients undergoing SCB PCI suggest MagicTouch SCB angioplasty is effective, with a low incidence of TLR, safe, as demonstrated by the low incidence of MACE, including cardiac death and MI, and might yield more favourable outcomes when treating *de novo* lesions than when treating ISR.

Notwithstanding the fact that only DES ISR patients were included in EASTBOURNE, our results in patients with ISR treated with SCBs are promising when compared to those of paclitaxel-coated balloons (PCBs), with a reported accrual of TLR events between 1- and 2-year follow-up (1.8%) lower than that reported in the DAEDALUS study (4.4%)[4]. In addition, despite a non-contemporary lesion predilation rate (only 89%) among *de novo* lesions, we report 2-year outcomes within a sample of lesions with a mean reference vessel diameter of 2.3 mm that compare favourably with those reported in randomised controlled trials of PCBs[5]. Nonetheless, failure to demonstrate the non-inferiority of the MagicTouch SCB for angiographic net lumen gain at 6 months compared to a PCB should be acknowledged[2]. Overall, these findings stress the need to raise awareness of the possible absence of a class effect in the antirestenotic performance of DCB technologies due to different drugs, excipients and catheter properties.

Selection bias and residual confounding bias when comparing *de novo* disease and ISR, notwithstanding multivariable adjustment, cannot be excluded because of the observational nature of our study. Underreporting or missing follow-up data in 10% of the study population need to be acknowledged. Also, core laboratory angiographic evaluation and quantitative coronary angiography were not available. The single-arm, open-label design of the study should be noted, though event adjudication was performed by an independent clinical events committee based on prespecified criteria after revision of the source documents. The fact that the results in the *de novo* lesions cohort represent mostly small coronary vessels needs to be highlighted, and the results might not be directly extrapolated to large vessels. Finally, the external validity of our study is limited by the fact that our results cannot be extrapolated to centres who have limited experience with DCB PCI.

EASTBOURNE – a multicentre, observational, prospective, investigator-driven study, including 2,123 all-comer patients with coronary artery disease – suggests MagicTouch SCB PCI is safe and effective, with low rates of clinically relevant adverse events at 2-year follow-up.

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Conflict of interest statement

B. Cortese has served as an advisory board member for Envision Scientific. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods: study characteristics, study device and procedure, follow-up and data management, endpoints and statistical analysis.

Supplementary Table 1. Baseline clinical and angiographic characteristics according to the type of lesion treated.

Supplementary Table 2. Predictors of target lesion revascularisation at 24-month follow-up after sirolimus-coated balloon angioplasty.

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Study characteristics

Exclusion criteria:

1) Patients with known (and untreatable) hypersensitivity or contra-indication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, sirolimus or contrast media;
2) Target lesion/vessel with any one of the following characteristics:
    (a) unsuccessful predilation 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 it;
    (c) highly tortuous culprit vessels;
    (d) visible thrombus at the lesion site, not treatable with manual aspiration.

Left main stem disease and ST-elevation myocardial infarction were eligible for enrollment. Each investigator involved in the study had to certify an adequate experience in DCB PCI by declaring utilization of at least 30 DCB/year in the last 5 years. The study received the approval of the central Ethical Committee of coordinating center (ASST FBF-Sacco, Milano: Comitato Etico Area B Milano, Italy), and thereafter from the Ethical Committees of all participating centers.\

Study device and procedure

Details on Magic Touch SCB have been previously described[1] (Cortese B, et al. Magic Touch®: preliminary clinical evidence with a novel sirolimus drug coated balloon. *Minerva Cardioangiol*. 2018;66:508-17). PCI was performed according to international consensus documents (Jeger RV, et al. Long-term efficacy and safety of drug-coated balloons versus drug-eluting stents for small coronary artery disease (BASKET-SMALL 2): 3-year follow-up of a randomised, non-inferiority trial. *Lancet.* 2020;396:1504-10 and Cortese B, et al. Drug-coated balloon treatment of coronary artery disease: a position paper of the Italian Society of Interventional Cardiology. *Catheter Cardiovasc Interv*. 2014;83:427-35).

Lesion preparation was performed with any type of device deemed necessary by the operator. Recommended inflation time is 60 seconds, with a minimum of 30 seconds. A balloon length exceeding at least 3 mm the lesion proximally and distally was recommended, and, if needed, multiples SCB were allowed. Bailout stenting was discouraged unless in presence of flow limiting dissection (TIMI flow <3) or acute vessel recoil after a minimum of 5 minutes from drug application. In case of stenting, DES implantation was recommended. Angiographic evaluation by visual estimation and antithrombotic regimen were left at operator's discretion. A minimum of 30-day DAPT was suggested in case of stable coronary disease, while a regimen of 6-12 months was indicated in case of ACS or bailout stenting.

Follow-up and data management

All patients were followed up clinically, with planned visits at 6 and 12 months from index procedure and a further clinical evaluation at 24 months. Final study follow-up is planned at 36-month. Angiographic surveillance or stress tests are not required by protocol, but dictated by clinical reasons only. A dedicated committee validated the quality of data input in the eCRF, and all events and study endpoints were adjudicated by an independent centralized clinical event committee, which had access to source documents.

Endpoints

Secondary endpoints at 2-year follow-up were incidence of major adverse cardiovascular events (MACE), a composite of cardiac death, spontaneous MI and TLR, and each of its single components. Furthermore, definite/probable vessel closure was defined according to the Academic Research Consortium criteria (Cutlip DE, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007; 115:2344–51). Procedural success was defined as a compound of angiographic success (TIMI flow grade 3 with percent diameter stenosis <30%) and absence of in-hospital complications. Outcomes were assessed in the overall population and comparing de novo lesions vs. ISR.

Statistical analysis

Continuous variables are reported as mean ± standard deviation or median ± interquartile range, and were compared using Student's t-test or Mann-Whitney U test in case of 2-group

comparisons on the basis of normality of data distribution, verified using the Shapiro-Wilk test. Categorical variables are reported as number (percentage) and were compared using the chi-square test without Yates' correction for continuity or the Fisher exact test, as appropriate. Unadjusted survival curves for TLR were constructed with the use of Kaplan–Meier estimates and compared with the log-rank test. Unadjusted and adjusted Cox proportional hazards models were generated for TLR outcome at 24-month follow-up. Hazard ratios (HRs) and 95% CIs are reported. The adjusted model includes characteristics we considered relevant: lesion type, patient sex, hypertension, previous myocardial infarction, previous coronary artery bypass grafting, previous PCI, multivessel disease, number of lesions treated, reference vessel diameter, minimal lumen diameter, balloon diameter, timing of stent implantation. Ten percent statistically significant parameters in univariable analysis ($p < 0.100$) were analyzed in multivariable analysis. Clinical follow-up was censored at the date of death or latest available follow-up. Data for patients lost to follow-up were censored at the time of the last contact. All tests were two-tailed and p-value <0.05 was considered significant. All statistical analyses were performed using R version 4.0.1 (R Core Team 2022. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Supplementary Table 1. Baseline clinical and angiographic characteristics according to the type of lesion treated.

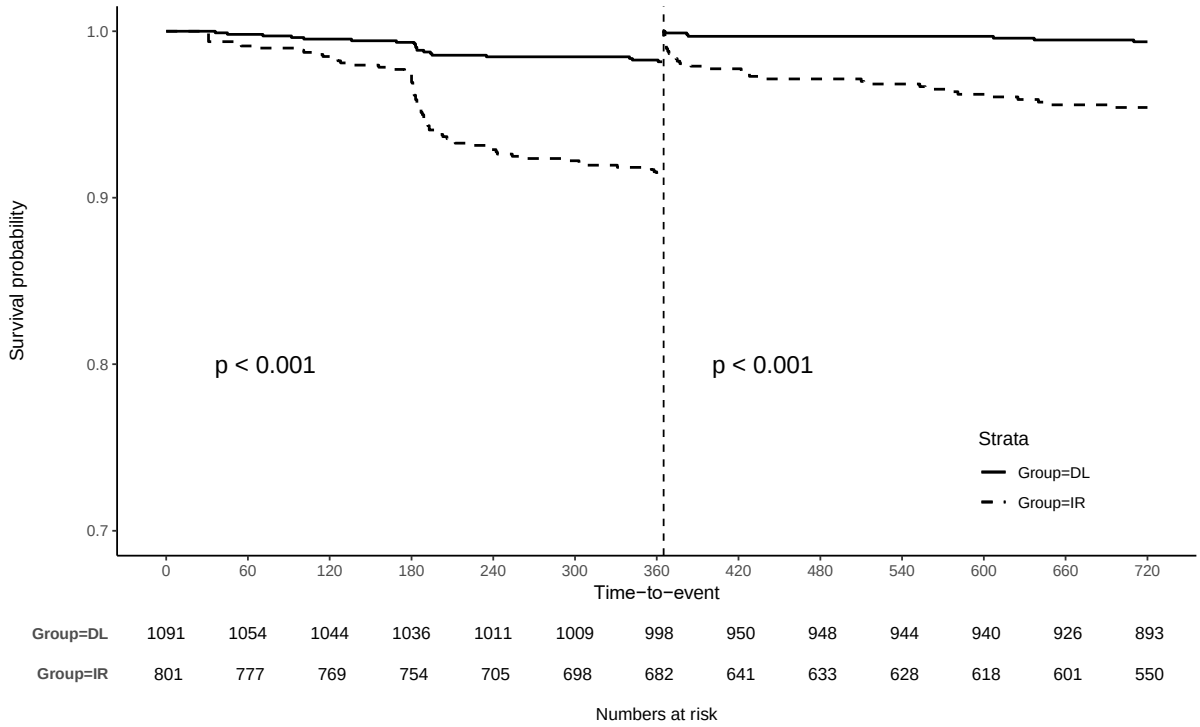
Variables	Overall cohort (n=2083)	De novo lesions (n=1173)	ISR (n=910)	P value
Age, years	66.6 ± 11.3	64.7 ± 11.8	69.1 ± 10.0	**<0.001**
Female	393 (18.9)	216 (18.4)	177 (19.5)	0.587
Arterial hypertension	1604 (77.0)	840 (71.6)	764 (84.0)	**<0.001**
Diabetes mellitus	864 (41.5)	452 (38.5)	412 (45.3)	**0.002**
Insulin-dependent diabetes mellitus	283 (13.6)	120 (10.2)	163 (17.9)	**<0.001**
Dyslipidaemia	1496 (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	1235 (59.3)	631 (53.8)	604 (66.4)	**<0.001**
LVEF, %	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	1380 (66.3)	503 (42.9)	910 (100)	**<0.001**
Previous CABG	244 (11.7)	81 (6.9)	163 (17.9)	**<0.001**
Clinical indication to PCI				**<0.001**
NSTEMI	445 (21.4)	257 (21.9)	188 (20.7)	
STEMI	159 (7.7)	127 (10.8)	32 (3.5)	
Unstable angina	364 (17.5)	156 (13.3)	208 (22.9)	
Stable CAD	1115 (53.5)	633 (54.0)	482 (52.9)	
	Overall cohort (n=2339)	**De novo lesions (n=1284)**	**ISR (n=1055)**	**P value**
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				**0.003**
Mild/None	47.0	35.1	67.4	
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**
Predilation balloon diameter, 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)	1.000
Stent implantation after DCB	181 (7.7)	112 (8.7)	69 (6.5)	0.059
Procedural success	2284 (97.6)	1242 (96.7)	1042 (98.8)	**0.002**

Values are mean ± standard deviation, median [interquartile range] or n(%). The values in **bold** represent differences between groups with p <0.100. Procedural success was defined as a compound of angiographic success without in-hospital complications. CABG = coronary artery bypass grafting; CAD = coronary artery disease; DCB = drug-coated balloon; ISR = in-stent restenosis; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLD = minimal lumen diameters; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; STEMI = ST elevation myocardial infarction.

Supplementary Table 2. Predictors of target lesion revascularisation at 24-month follow-up after sirolimus-coated balloon angioplasty.

Variables	Univariable HR	95% CI	P value	Multivariable HR	95% CI	P value
ISR	5.44	3.53-8.39	**<0.001**	4.39	2.52-7.63	**<0.001**
Age, per year	1.01	1.00-1.03	0.109			
Male	0.61	0.41-0.91	**0.016**	0.60	0.40-0.90	**0.013**
Arterial hypertension	1.88	1.14-3.09	**0.014**	1.26	0.75-2.10	0.377
Diabetes mellitus	1.32	0.93-1.87	0.122			
Insulin-dependent diabetes mellitus	1.35	0.85-2.16	0.207			
Dyslipidaemia	1.16	0.78-1.75	0.461			
Congestive Heart Failure	1.51	0.86-2.63	0.148			
Multivessel disease	1.80	1.22-2.65	**0.003**	1.30	0.87-1.93	0.206
LVEF, %	0.99	0.97-1.01	0.376			
Previous MI	1.77	1.25-2.52	**0.001**	1.07	0.74-1.56	0.709
Previous PCI	4.08	2.38-7.00	**<0.001**	1.36	0.68-2.71	0.386
Previous CABG	2.24	1.46-3.43	**<0.001**	1.53	0.99-2.38	0.055
RVD, per mm	1.20	1.03-1.40	**0.021**	0.93	0.75-1.15	0.486
Lesion length, per mm	0.99	0.97-1.01	0.467			
MLD, per mm	0.65	0.47-0.89	**0.008**	0.52	0.37-0.73	**<0.001**
Lesion predilation	1.87	0.82-4.24	0.136			
SCB diameter, per mm	1.03	1.01-1.06	**0.021**	1.06	1.02-1.10	**0.006**
Stent implantation						
None	-	-	-	-	-	-
Pre-SCB	1.29	0.53-3.15	0.581	1.12	0.45-2.78	0.803
Post-SCB	0.70	0.33-1.51	0.368	0.76	0.35-1.63	0.481
>1 lesion treated	2.14	1.56-2.93	**<0.001**	1.99	1.43-2.79	**<0.001**

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ration; ISR = in-stent restenosis; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; SCB = sirolimus-coated balloon.



Supplementary Figure 1. Kaplan-Meier estimates of target lesion revascularisation according to lesion type with a landmark analysis at 1-year follow-up.

DL = de novo lesions; IR = in-stent restenosis