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ORIGINAL RESEARCH

Sirolimus-Eluting Balloon vs Repeat Drug-Eluting Stent or Balloon Angioplasty for Coronary In-Stent Restenosis

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ABSTRACT

BACKGROUND Drug-eluting stents (DESs) are recommended treatment for coronary in-stent restenosis (ISR) but are not used in >20% of cases.

OBJECTIVES The aim of the SELUTION4ISR (SELUTION SLR 014 In-stent Restenosis) trial was to assess the safety and effectiveness of a novel sirolimus drug-eluting balloon (DEB).

METHODS After successful lesion predilation, patients with ISR were randomly assigned to the SELUTION Sustained Limus Release (MedAlliance) DEB or a control strategy of usual care, including any approved DES or balloon angioplasty (BA) on the basis of operator selection prerandomization. Randomization to selected BA control treatment was limited to 20% of patients. The primary outcome was target lesion failure (TLF) (cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization) assessed at 1 year in the per protocol group (all treated eligible patients with complete primary endpoint follow-up). Noninferiority was established if the upper limit of the 2-sided 95% credible interval was smaller than 10%. A sequential secondary hypothesis test was performed comparing DEB with DES in patients with single-layer ISR.

RESULTS From July 2020 to July 2024, 418 patients were randomly assigned to the DEB group (n = 210) or the control group (n = 208), with 390 patients per protocol (DEB, 197; control, 193 [154 DES; 39 BA]). TLF occurred in 32 (16.2%) of 197 patients in the DEB group and in 28 (14.5%) of 193 patients in the control group (difference: 1.7%; 95% credible interval: −5.5% to 8.9%; posterior probability of noninferiority: 98.80%). In the secondary hypothesis test, TLF occurred in 22 (14.2%) of 155 patients in the DEB group and in 9 (6.5%) of 138 patients in the DES control group (difference: 7.7%; 95% credible interval: 0.6%-14.6%, posterior probability for noninferiority: 76.07%). TLF according to operator selected control was higher for DEB compared with DES (15.3% vs 7.1%; difference: 8.1%; 95% credible interval: 1.4%-15.0%) and lower for DEB compared with BA (23.6% vs 43.6%; difference: 23.7%; 95% credible interval: −41.4% to −1.5%; $P_{\text{for interaction}} = 0.0026$).

CONCLUSIONS The sirolimus DEB was noninferior to a usual care control strategy including 80% repeat DES but not noninferior to DES for single-layer ISR for TLF at 12 months. There was significant interaction on the basis of operator selection of DES vs BA. (SELUTION SLR 014 In-stent Restenosis [SELUTION4ISR]; NCT04280029)
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Contemporary coronary drug-eluting stents (DESs) have lower coronary in-stent restenosis (ISR) compared with bare-metal stents (BMSs) and first-generation DESs. However, ISR requiring repeat revascularization or associated with myocardial infarction (MI) occurs in 4% to 8% of patients within 1 year,[1,2] and it continues with an annual hazard of 1% to 1.2% per year.[3,4] From 2011 to 2017, data from the National Cardiovascular Data Registry showed that 10.6% of all percutaneous coronary interventions in the United States were performed for treatment of ISR.[5]

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Repeat stenting using contemporary DESs has demonstrated superiority over plain balloon angioplasty (BA), brachytherapy, and BMS for prevention of recurrent ISR, thus reducing recurrent restenosis from >30% for BA to <10% for contemporary DES.[6-9] Despite this overwhelming benefit of repeat DES use, there are concerns about placement of multiple layers of metallic stents, including an increased risk for neoatherosclerosis, recurrent target lesion revascularization, loss of vasomotor reactivity, and late thrombosis.[10-12] In the previously mentioned National Cardiovascular Data Registry report,[5] repeat DESs were used in only 77% of cases. Although paclitaxel-coated balloons have shown superior results compared with BA, they have been inferior to repeat DES use for treatment of DES ISR.[7,8,13,14] Sirolimus as an alternative agent for balloon catheter delivery is of interest given a broad therapeutic window, but development has been delayed by technical challenges for drug delivery and tissue uptake.[15] We designed the SELUTION4ISR (SELUTION SLR 014 In-stent Restenosis; NCT04280029) clinical trial to assess safety and effectiveness of a novel sirolimus-eluting balloon compared with a contemporary standard of care in the United States that included selected use of repeat DESs or BA for coronary ISR.

METHODS

STUDY DESIGN. SELUTION4ISR is a multicenter, single-blind, active treatment, controlled clinical trial conducted at 48 sites in 7 countries. The trial design has been published previously.[16] The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the Institutional Review Board or Ethics Committee at each center. All patients provided written informed consent. A steering committee developed and approved amendments to the study protocol and had oversight of development of the statistical analysis plan, patient recruitment and follow-up, and data analysis. The trial is registered with ClinicalTrials.gov (NCT04280029). The trial has completed enrollment and 1-year follow-up of the primary endpoint. Clinical follow-up is to be performed in all patients through 5 years and is ongoing.

PATIENTS. Patients aged 18 years or older with myocardial ischemia who underwent percutaneous coronary intervention for a single lesion within a previous BMS or DES in a native coronary artery were eligible for enrollment. Each lesion was required to be no more than 26 mm in length, with a reference vessel diameter 2.0 to 4.5 mm on visual assessment. Patients with >2 previous layers of stent at any segment of the target lesion were excluded. Successful lesion preparation using any approved device with residual stenosis not >30% and without dissection more than National Heart, Lung, and Blood Institute type C was required before

ABBREVIATIONS AND ACRONYMS

BA = balloon angioplasty
BMS = bare metal stent
DAPT = dual antiplatelet therapy
DEB = drug-eluting balloon
DES = drug-eluting stent
ISR = in-stent restenosis
ITT = intention to treat
MI = myocardial infarction
TLF = target lesion failure

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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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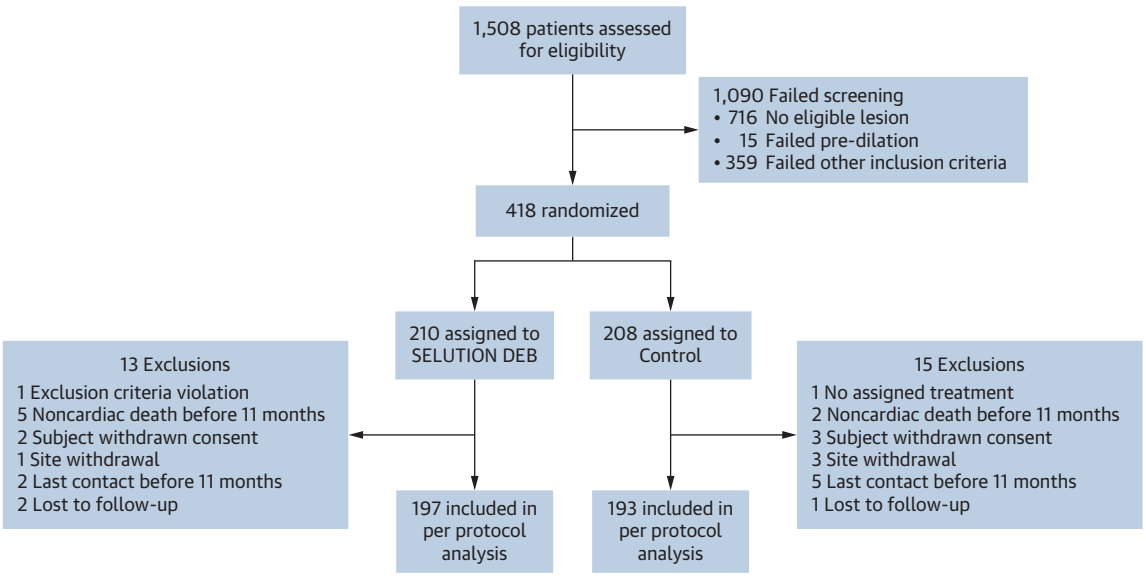
FIGURE 1 Study Profile



Consent was obtained from patients before diagnostic coronary angiography, and patients were excluded if an eligible in-stent restenosis lesion was not found. The requirement for successful lesion preparation failed in only 15 patients. The per protocol group comprised the primary analysis and excluded patients missing at least 11 months of primary endpoint follow-up. All randomized patients were included in the intention-to-treat analysis, with analyses for missing data including time to event, multiple imputation, and tipping point. DEB = drug-eluting balloon.

randomization. The full list of trial inclusion and exclusion criteria is provided in the Supplemental Appendix.

RANDOMIZATION AND MASKING. Eligible patients were randomly assigned (1:1) to receive the study device or control treatment. The control group was designed to approximate usual care in the United States on the basis of the National Cardiovascular Data Registry from 2009 to 2017,[5] including either contemporary DES (everolimus-eluting or zotarolimus-eluting stent) in 80% of patients or BA in up to 20% on the basis of operator decision before randomization. Selected use of BA in the control group was stopped after reaching 20% of projected enrollment. Randomization assignments were allocated using the study electronic data capture system in random block sizes stratified by study center, BMS or DES ISR, and 1 or 2 previous stent layers. We did not stratify by operator selection of control strategy, given the anticipated early discontinuation of randomization to BA (only 42 BA patients allowed) and to avoid very small strata with 4 stratification variables. A subset of 30 patients in each group will be followed up for routine angiographic and optical coherence tomography follow-up. This analysis will be reported separately.

PROCEDURES. All patients received a loading dose of at least 150 mg aspirin within 24 hours before the procedure. A loading dose of a $P2Y_{12}$ receptor antagonist was administered before the procedure or within 1 hour after the procedure. Intracoronary imaging using intravascular ultrasound or optical coherence tomography was required to assess vessel size and confirm adequate stent expansion.

The study device is the SELUTION Sustained Limus Release (SLR) Drug-Eluting Balloon (DEB, MedAlliance, a Cordis Company). It is a combination product consisting of a standard percutaneous transluminal angioplasty balloon catheter coated with sirolimus at 1 $\mu g/mm^2$. The drug coating is formulated with sirolimus loaded into polylactic-co-glycolic acid microspheres suspended in a phospholipid blend designed to allow for sustained elution of sirolimus over a period of approximately 90 days.[17] An adherent phospholipid layer protects the microspheres during catheter delivery and allows prolonged contact with the vessel wall. Preliminary data have not shown safety concerns and suggest favorable angiographic outcomes.[18] A study device with a nominal diameter 1.0 to 1.1 times the reference vessel diameter was inflated at nominal pressure for a goal of 60 seconds and a minimum of 30 seconds.

Additional BA or intracoronary imaging after DEB deployment was not permitted to avoid disruption of the adherent amphipathic lipid carrier.

If a participant was selected for BA, then only additional BA could be performed if indicated on the basis of visual assessment of angiography or repeat intracoronary imaging. If a participant was selected for DES, then DES implantation was performed according to local site standards. Postdilation and repeat intracoronary imaging after DES were recommended.

Final angiography was required in all patients. Stenting in the BA or DEB groups was advised on the basis of angiographic visual assessment of residual stenosis >50% or residual dissection more than National Heart, Lung, and Blood Institute grade C.

Dual antiplatelet therapy (DAPT) was recommended for 6 months after DES and 1 month after BA or DEB. DAPT could be shortened to 1 or 3 months according to regional guidelines for patients at high bleeding risk, and aspirin could be discontinued in favor of a $P2Y_{12}$ receptor antagonist alone in patients requiring uninterrupted oral anticoagulation therapy.

Patients were followed up at 1, 6, and 12 months for reporting of study endpoints and adverse events.

OUTCOMES. The primary endpoint was target lesion failure (TLF) (including cardiac death, target vessel MI, or clinically driven target lesion revascularization) assessed at 1 year. MI was defined according to the Society for Cardiac Angiography and Intervention for periprocedural events and according to the Fourth Universal Definition for postprocedure events.[19,20] Secondary endpoints included the components of the primary endpoint and safety endpoints of stent or lesion thrombosis and bleeding. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium and for this study included the segment of treatment with an additional stent, DEB, or BA.[21] Bleeding was defined according to Bleeding Academic Research Consortium types 2 to 5.[22] Results of procedural quantitative coronary angiography were determined by an independent core laboratory. The target lesion was defined as the segment undergoing treatment with stenting or angioplasty in addition to 5 mm proximally and distally. Detailed endpoint and protocol definitions and all prespecified secondary endpoints are listed in the Supplemental Appendix. All primary and secondary endpoints were adjudicated by an independent clinical events committee whose members were unaware of trial group assignments.

TABLE 1 Baseline Clinical and Lesion Characteristics of the Study Population

	DEB Group (n = 197)	Control Group (n = 193)
Median age, y	68 (63-75)	71 (63-76)
Sex		
Male	161 (82)	143 (74)
Female	36 (18)	50 (26)
Medical history		
Diabetes mellitus	85 (43)	82 (43)
Hypertension	183 (93)	180 (93)
Hypercholesterolemia	179 (91)	171 (89)
Previous myocardial infarction	94 (48)	93 (48)
Current or former smoker	113 (57)	107 (55)
Current smoker	30 (15)	27 (14)
Number of previous stents at target lesion		
1	153 (78)	151 (78)
2	44 (22)	42 (22)
Previous DES at target lesion	174 (88)	177 (92)
Target lesion location		
Left anterior descending artery	78 (40)	76 (39)
Circumflex artery	50 (25)	45 (23)
Right coronary artery	68 (35)	65 (34)
Lesion length, mm	10.6 (8.2-15.7)	10.2 (7.7-15.9)
Reference vessel diameter, mm	2.5 (2.2-2.8)	2.6 (2.4-3.0)
Minimum lumen diameter, mm	0.9 (0.6-1.1)	0.9 (0.6-1.1)
Percent diameter stenosis	63.9 (56.5-73.8)	63.7 (57.1-74.1)

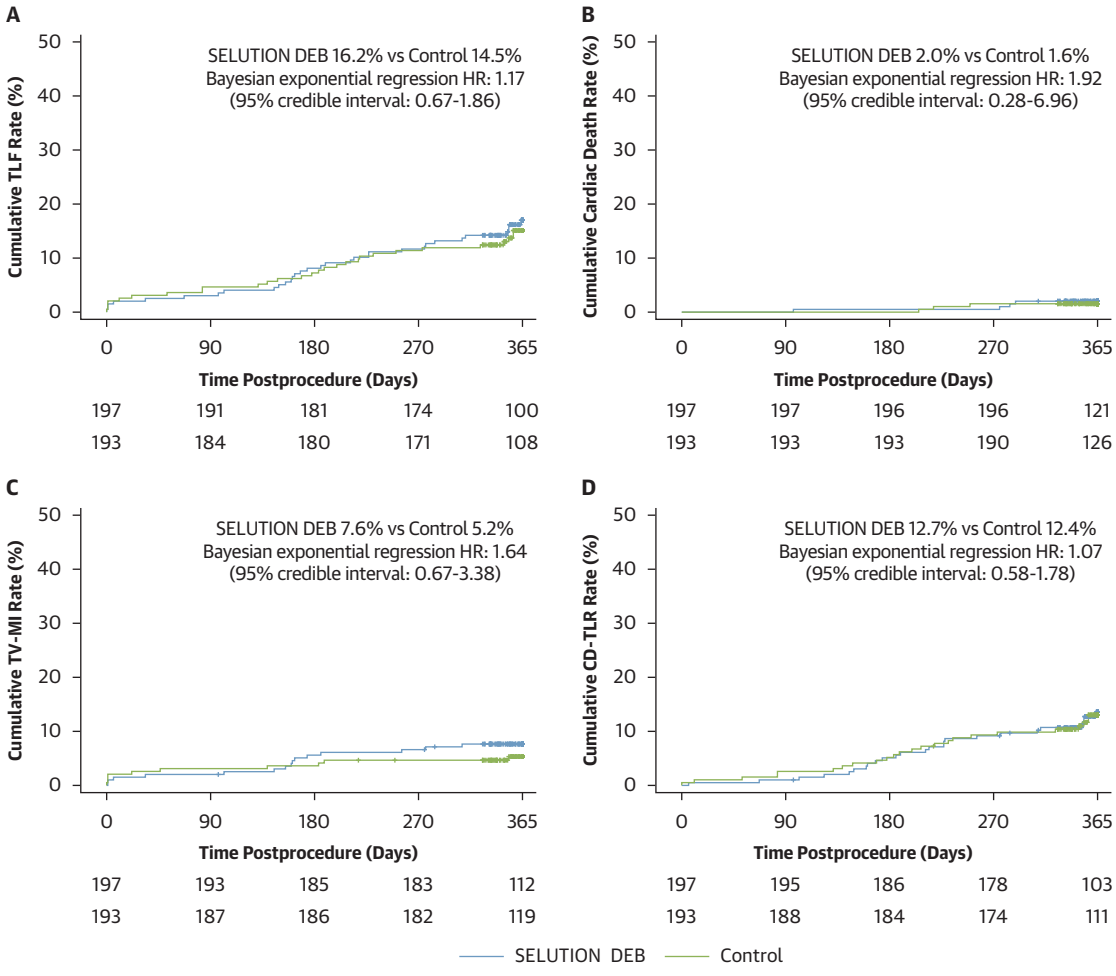
Data are n (%) or median (Q1-Q3).
DEB = SELUTION Sustained Limus Release drug-eluting balloon (MedAlliance).

TABLE 2 Procedure Results and Angiographic Outcomes

	DEB Group (n = 197)	Control Group (n = 193)
Prerandomization treatment		
Devices used		
Intracoronary imaging	193 (98)	190 (98)
Plain balloon angioplasty	172 (87)	162 (84)
Cutting or scoring balloon	87 (44)	102 (53)
Maximum inflation pressure, atm	18 (15-20)	18 (14-22)
Minimum lumen diameter, mm	1.9 (1.6-2.2)	1.9 (1.6-2.2)
Percent diameter stenosis	23.8 (15.4-31.1)	22.8 (15.2-31.8)
Poststudy device		
Maximum device length, mm	20.0 (15.0-30.0)	18.0 (15.0-24.0)
Maximum balloon diameter, mm	3.5 (3.0-3.5)	3.0 (3.0-3.5)
Maximum inflation pressure, atm	10 (6-14)	16 (12-18)
Number of new stents		
1	3 (1.5)	146 (75.6)
2	0 (0)	8 (4.1)
Minimum lumen diameter, mm, mean ± SD	2.3 (1.9-2.6)	2.5 (2.1-2.9)
Percent diameter stenosis, %, mean ± SD	15.6 (9.7-22.4)	11.4 (6.2-15.7)

Data are n (%) or median (Q1-Q3).
DEB = SELUTION Sustained Limus Release drug-eluting balloon (MedAlliance).

FIGURE 2 Time-to-Event Curves for the Primary Endpoint and Components (Per Protocol Population)



Time-to-event curves are shown for (A) target lesion failure (TLF), (B) cardiovascular death, (C) target vessel myocardial infarction (TV-MI), and (D) clinically driven target lesion revascularization (CD-TLR) among patients randomly assigned to receive the SELUTION (MedAlliance) drug-eluting balloon or control therapy, including a drug-eluting stent or balloon angioplasty. Comparison between the groups was based on Bayesian exponential regression and was reported as HR and 95% credible interval.

STATISTICAL ANALYSIS. Noninformative Bayes methods were prespecified for analysis of the primary endpoint. Noninferiority was determined by comparing the upper bound of the 95% credible interval on the difference between treatment and control with a noninferiority margin of 10%. We chose a noninferiority margin of 10% on the basis of an estimated minimum difference of >20% for DES vs BA from previous trials,[6-8,23-30] limited enrollment of 20% BA-treated patients, and the substantial clinical benefit associated with avoiding additional layers of metallic stent. Sample size for the noninferiority analysis was estimated on the basis of assumptions of 12% TLF in each group, 97.5% posterior probability for the alternative hypothesis, 5% lost to follow-up, and power of 85%. Accordingly, 418 patients were required for enrollment. When the primary endpoint analysis for noninferiority was successful, then a sequential secondary hypothesis test was performed comparing DEB vs DES in those patients with a single layer of previous stent for noninferiority. Given the noninferiority design, a per protocol group was used for the primary analysis to reduce the bias to noninferiority associated with intention to treat (ITT) when protocol deviations, crossovers, or nonadherence would occur.

Per protocol criteria were prespecified as receiving treatment without major inclusion criteria violations and completing at least 330 days of follow-up or sustaining a primary endpoint event. The analysis was

also performed in the intention-to-treat (ITT) group including all randomized patients. Exploratory analyses comparing the primary and secondary endpoints for DEB vs DES and DEB vs BA on the basis of selected control patients as treated were also performed.

Baseline clinical and lesion characteristics are presented for DEB vs control treatment and for DEB vs DES or BA according to the control treatment. Summaries of continuous variables are presented as mean ± SD or median (Q1-Q3). The primary endpoint is presented by a comparison of proportions using known nonmissing values and is reported as difference, 2-sided 95% credible interval, and posterior probability of noninferiority. Secondary clinical endpoints are reported as difference, 2-sided 95% credible intervals, and estimated *P* value on the basis of posterior probability of difference more than 0. Difference between treatments is calculated using Bayesian methods on the basis of noninformative prior.

Analysis of the primary endpoint was also conducted in prespecified subgroups defined according to age, sex, diabetes, lesion length, vessel diameter, BMS vs DES ISR, and 1 vs 2 layers of previous stent. Results are presented as differences and 95% credible intervals. A test of interaction was performed to assess formally the heterogeneity of treatment effect.

Time-to-event analyses are shown for the primary endpoint of TLF and the components of cardiac death, target vessel MI, and clinically driven target lesion revascularization in the per protocol and ITT groups. The cumulative incidence curves are compared using Bayesian exponential regression. In the ITT group, patients with noncardiac death or loss to follow-up were censored at time of death or last contact. In separate analyses, noncardiac death was assessed as a competing risk.

Missing data in the ITT group are analyzed using a Bayesian imputation model and tipping point analysis in addition to the foregoing time-to-event analysis.

An independent data monitoring committee, composed of experts who were independent from the sponsors and not included as authors, monitored safety and efficacy throughout the trial.

All descriptive statistical analyses were performed using SAS for Windows software version 9.4 or later (SAS Institute). Bayesian analyses were performed using the open-source application Just Another Gibbs Sampler (JAGS) version 4.3.

RESULTS

Between July , 2020 and July 16, 2024, a total of 1,508 patients were screened at 48 clinical sites. Of these patients, 418 were randomly assigned to receive DEB (n = 210) or control treatment (n = 208). Screen failure in 1,090 patients resulted from the absence of an eligible lesion at the time of angiography (n = 716), residual stenosis >30% (n =15), and other inclusion or exclusion violations (n = 359). The other reasons for exclusion are included in Supplemental Table 1. The maximum allowed BA cohort was reached after 176 (42%) patients were assigned treatment; subsequent patients were randomly assigned to DEB or DES. There were 28 patients excluded from the per protocol group, leaving 390 patients (DEB, 197; control, 193) in the primary analysis (**Figure 1**).

BASELINE CHARACTERISTICS AND PROCEDURAL OUTCOMES. The baseline clinical and lesion characteristics for the per protocol population are presented in **Table 1**. The median age was 69 years (Q1-Q3: 63-75 years), 22% were women, and 43% had a history of diabetes. Two-layer ISR was present in 22% of patients. The baseline characteristics for the ITT group and for the cohorts receiving DES or BA control treatment are presented in Supplemental Tables 2 and 3. Baseline characteristics were not significantly different for the 28 patients excluded from the per protocol group.

The procedural results and angiographic outcomes for lesion preparation before and after study device treatment are presented in **Table 2**. In accordance with the protocol, 98% of patients in each group underwent intracoronary imaging. Treatment with cutting or scoring balloon was performed in 44% of the DEB group and in 53% of control patients. The minimum lumen diameter and percentage of diameter stenosis were similar for the DEB and control groups after lesion preparation, but after study device, minimum lumen diameter was larger and percentage of diameter stenosis was smaller for the control group. The results for the cohorts receiving DES or BA control treatment are presented in Supplemental Table 4. Of 40 patients intended for BA, 2 received DES because of operator decision, without bailout criteria. Of 153 patients intended for DES, 1 underwent BA only as a result of failed stent delivery.

OUTCOMES. In the per protocol group at 12 months, TLF occurred in 32 (16.2%) of 197 patients in the DEB group and in 28 (14.5%) of 193 patients in the control group (difference: 1.7%; 95% credible interval: −5.5% to 8.9%; posterior probability of noninferiority: 98.80%), finding that met the noninferiority criterion. Consistent results for the primary endpoint were found for the ITT group in which TLF occurred in 32 (15.2%) of 210 patients in the DEB group and in

TABLE 3 Primary and Secondary Endpoints for Per Protocol Analysis at 1 Year

Endpoint	DEB Group (n = 197)	Control Group (n = 193)	Difference[a] (95% Credible Interval), %	Bayesian Estimated *P* Value[b]
Target lesion failure	32 (16.2)	28 (14.5)	1.7 (−5.5 to 8.9)	0.90
Cardiac death	4 (2.0)	3 (1.6)	0.5 (−2.5 to 3.5)	0.86
Target vessel myocardial infarction	15 (7.6)	10 (5.2)	2.4 (−2.5 to 7.4)	0.34
Periprocedural	2 (1.0)	4 (2.1)	−1.1 (−4.0 to 1.7)	0.43
Postprocedure	13 (6.6)	7 (3.6)	2.9 (−1.5 to 7.6)	0.19
Any target lesion revascularization	27 (13.7)	26 (13.5)	0.2 (−6.6 to 7.0)	0.95
Clinically driven target lesion revascularization	25 (12.7)	24 (12.4)	0.2 (−6.4 to 6.9)	0.94
Target vessel revascularization[c]	33 (16.8)	28 (14.5)	2.2 (−5.0 to 9.4)	0.55
Nontarget vessel revascularization	14 (7.1)	13 (6.7)	0.4 (−4.8 to 5.5)	0.89
Stent (lesion) thrombosis	4 (2.0)	4 (2.1)	−0.0 (−3.2 to 3.1)	0.98
Definite	2 (1.0)	3 (1.6)	−0.5 (−3.3 to 3.1)	0.67
Probable	2 (1.0)	1 (0.5)	−0.5 (−1.7 to 2.8)	0.64
Bleeding (BARC 2-5)	15 (7.6)	18 (9.3)	−1.7 (−7.4 to 3.9)	0.55
BARC 3	5 (2.5)	7 (3.6)	−1.1 (−4.9 to 2.5)	0.55
BARC 5	0 (0)	1 (0.5)	−0.5 (−2.5 to 1.1)	0.49

Values are n (%) unless otherwise indicated. [a]Difference between treatments is calculated using Bayesian methods on the basis of noninformative prior. [b]Bayesian *P* value calculated as 2 times the minimum of the Bayesian posterior probability for difference <0 and difference >0. [c]Includes any target lesion revascularization and any other site within the target vessel.

BARC = Bleeding Academic Research Consortium; DEB = SELUTION Sustained Limus Release drug-eluting balloon (MedAlliance).

28 (13.5%) of 208 patients in the control group (difference: 1.8%; 95% credible interval: −5.0% to 8.5%; posterior probability for noninferiority: 99.18%).

In the secondary hypothesis test of DEB vs DES among patients with single-layer ISR, TLF occurred in 22 (14.2%) of 155 patients in the DEB group and in 9 (6.5%) of 138 patients in the control group (difference: 7.7%; 95% credible interval: 0.6%-14.6%; posterior probability for noninferiority: 76.07%), findings that did not meet the criterion for noninferiority.

The cumulative incidences of the primary endpoint and components are shown in **Figures 2A to 2D** for the per protocol group. Results for ITT are similar to per protocol and are presented in Supplemental Figures 1A to 1D. All secondary endpoints are shown in **Table 3** for the per protocol group. Periprocedural MI occurred in 2 (1.0%) of 197 patients in the DEB group and in in 4 (2.1%) of 193 patients in the control group. Definite or probable stent or lesion thrombosis occurred in 4 (2.0%) of 197 patients in the DEB group and in 4 (2.1%) of 193 patients in the control group. Secondary endpoints for ITT are shown in Supplemental Table 5.

Among the prespecified subgroups, there were no significant treatment by subgroup interactions for the primary endpoint for the per protocol group (**Figure 3A**). However, there was a significant interaction for operator selection of DES or BA control treatment (**Figure 3B**). Among patients with DES control, TLF occurred in 25 (15.3%) of 163 patients in the DEB group and in 11 (7.1%) of 154 patients in the DES group (difference: 8.1%; 95% credible interval: 1.4%-15.0%). Among patients with BA control, TLF occurred in 7 (23.6%) of 34 patients in the DEB group and in 17 (43.6%) of 39 patients in the BA group (difference: −23.7%; 95% credible interval: −41.4% to −1.5%). The detailed primary and secondary endpoints according to the control treatment of DES or BA are shown in Supplemental Tables 6 and 7. Results for the ITT group and details for heterogeneity by center are shown in Supplemental Figure 2 and Supplemental Table 8.

The primary endpoint according to control treatment and number of ISR layers is shown in **Table 4**. All treatments had a higher risk of recurrence for 2-layer ISR such that there was not a significant interaction for the treatment differences by number of previous stent layers.

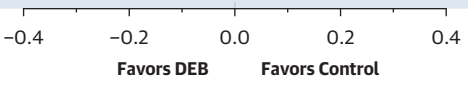
Despite differences in protocol recommendations, DAPT or $P2Y_{12}$ monotherapy remained high at 6 months in all treatment groups (Supplemental Table 9).

Missing data analyses, including multiple imputation and tipping point for the ITT group, are shown in Supplemental Tables 10 and 11. The multiple imputation model yielded an estimated absolute difference for DEB vs control of 1.4%, a 95% credible interval of −5.6% to 8.3%, and posterior probability of noninferiority of 99.1%.

FIGURE 3 Subgroup Analyses of the Primary Endpoint

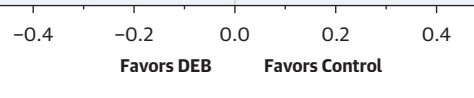
A

Subgroup	DEB	Control	Difference (95% Credible Interval)	Pint
Age				0.5663
>75	7/42 (17)	10/53 (19)	−0.02 (−0.17 to 0.14)	
≤75	25/155 (16)	18/140 (13)	0.03 (−0.05 to 0.11)	
Sex				0.8645
Female	6/36 (17)	7/50 (14)	0.03 (−0.12 to 0.19)	
Male	26/161 (16)	21/143 (15)	0.01 (−0.07 to 0.09)	
Medical History of Diabetes				0.4297
Diabetes	22/85 (26)	17/82 (21)	0.05 (−0.08 to 0.18)	
No Diabetes	10/112 (9)	11/111 (10)	−0.01 (−0.09 to 0.07)	
Reference Vessel Diameter				0.3706
>2.75	11/65 (17)	7/66 (11)	0.06 (−0.06 to 0.18)	
≤2.75	21/132 (16)	21/127 (17)	−0.01 (−0.10 to 0.08)	
Lesion Length				0.2825
<10 mm	14/87 (16)	17/90 (19)	−0.03 (−0.14 to 0.09)	
10-20 mm	14/86 (16)	8/77 (10)	0.06 (−0.05 to 0.16)	
>20 mm	4/23 (17)	2/23 (9)	0.08 (−0.12 to 0.28)	
Number of Stent Layers				0.2152
One	22/155 (14)	16/157 (10)	0.04 (−0.03 to 0.11)	
Two	10/42 (24)	12/36 (33)	−0.09 (−0.29 to 0.10)	



B

Subgroup	DEB	Control	Difference (95% Credible Interval)	Pint
Selected Control Treatment				0.0026
DES	25/163 (15)	11/154 (7)	0.08 (0.01-0.15)	
BA	7/34 (21)	17/39 (44)	−0.24 (-0.41 to −0.02)	



Subgroup analyses are shown, with risk difference between the SELUTION (MedAlliance) drug-eluting balloon (DEB) and control therapy, 95% credible interval, and calculated *P* value for interaction using Bayesian estimate for the primary end point of target lesion failure at 1 year. (A) Prespecified subgroups of patients randomly assigned to the drug-eluting balloon or control therapy, including a drug-eluting stent (DES) or balloon angioplasty (BA). (B) Operator-selected control treatment of a drug-eluting stent or balloon angioplasty in patients randomly assigned to drug-eluting balloon or control therapy.

DISCUSSION

In this randomized trial comparing a sirolimus DEB with a usual care control therapy (80% DES and 20% BA) approximating routine practice for BMS or DES ISR with 1 or 2 previous stent layers, the DEB was noninferior for the primary endpoint of TLF at 1 year. There were no differences in safety, with similar rates of mortality, MI, stent thrombosis, and bleeding in each group. The results of the primary endpoint for DEB vs control treatment were consistent for the primary per protocol analysis, ITT analysis, time-to-event analysis with noncardiac death as a competing risk, multiple imputation for missing data, and across several prespecified subgroups. However, for the prespecified secondary hypothesis, the DEB did not meet criteria for noninferiority compared with DES among patients with single-layer ISR.

Substantial interest and some urgency have been expressed for approval of drug-coated balloon technology for an ISR indication in the United States.

TABLE 4 Target Lesion Failure By Selected Control Treatment and Number of In-Stent Restenosis Stent Layers

	Selected DES Control Treatment				Selected BA Control Treatment			
Layers	DEB (n = 163)	DES (n =154)	Difference[a] (95% Credible Interval), %	*P* for Interaction	DEB (n = 34)	BA (n =39)	Difference[a] (95% Credible Interval), %	*P* for Interaction
Single	18/137 (13.9)	9/138 (6.5)	7.27 (0.15-14.63)	0.92	3/18 (16.7)	7/19 (36.8)	−18.14 (−44.16 to 8.82)	0.98
Double	6/26 (23.1)	2/16 (12.5)	8.3 (−15.89 to 30.62)		4/16 (25.0)	10/20 (50.0)	−22.28 (−49.67 to 7.3)	

Values are number of events/denominator (%) unless otherwise indicated. [a]Difference between treatments is calculated using Bayesian methods on the basis of noninformative prior.
BA = balloon angioplasty; DEB = SELUTION Sustained Limus Release drug-eluting balloon (MedAlliance); DES = drug-eluting stent.

Although repeat DES is recognized as the most effective treatment for prevention of recurrent ISR and the only treatment with a Class IA recommendation by both the European Society of Cardiology and the American Heart Association/American College of Cardiology guidelines,[31,32] there remains reluctance to place additional stents because of the higher risk of future adverse ischemic events after repeat DES for ISR.[10-12] Thus, before recent approval of the AGENT paclitaxel-coated balloon (Boston Scientific), plain BA had emerged as a common alternative in the United States, despite its known poor performance. Indeed, AGENT was approved on the basis of demonstration of superiority to BA without data vs DES.[14,33]

The SELUTION DEB is the first sirolimus-coated balloon to be tested for regulatory approval for treatment of ISR in the United States and the first drug-coated balloon to be tested against a usual care control strategy for such approval. The blended control group of 80% DES and 20% BA was selected to mirror the standard of care in the United States at the time of enrollment and was the primary comparator against which noninferiority was based. However, the inclusion of both BA and DES control treatments allows secondary comparisons that have implications for clinical practice. The allowance of BA provided for inclusion of 22% patients with multilayer ISR. Although this percentage is lower than the 44% patients with multilayer ISR included in the AGENT IDE (A Clinical Trial to Assess the Agent Paclitaxel Coated PTCA Balloon Catheter for the Treatment of Subjects With In-Stent Restenosis; NCT04647253) trial,[33] it is higher than if DES were the only control option and allows demonstration of safety and effectiveness of the DEB study device in these more complex lesions. In the group with DEB vs BA treatment, there were 50% of patients with 2-layer ISR. DEB resulted in 50% reduction in TLF and TLR, thus suggesting that failure of inhibition of neointimal hyperplasia is a predominant mechanism for BA failure.

The secondary comparison of DEB vs DES is especially important. Even though, as expected, selection of DES was limited almost exclusively to single-layer ISR, the outstanding performance of DES in this subgroup has clinical implications for treatment of initial ISR. Our results are consistent with those of trials comparing DES with paclitaxel-coated balloons for treatment of DES ISR.[8,13] Among 309 patients randomized in RIBS IV (Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent; NCT01239940), the 1-year composite of cardiac death, MI, or target vessel revascularization was significantly lower for DES (10% vs 18%; $P = 0.04$).[8] In the DAEDALUS (Difference in Antirestenotic Effectiveness of Drug-Eluting Stent and Drug-Coated Balloon Angioplasty for the Occurrence of Coronary In-Stent Restenosis) meta-analysis, DES was superior to drug-coated balloon for treatment of DES ISR for 1-year target lesion revascularization (13.4% vs 20.3%; $P = 0.002$).[13] The difference of 7.7% for DES vs DEB for single-layer ISR in our study supports the view that DES may be the preferred option for treatment of an initial ISR when feasible. However, the long-term effect of the first added layer of stent still requires ongoing follow-up, and some clinicians and patients may accept a higher rate of recurrence to avoid a second layer of stent and risk for multilayer ISR as part of a lifetime management strategy.[34] Early closure of the BA randomization and inclusion of almost 50% single-layer ISR in the BA group in our study highlight this potential concern. Ongoing follow-up of the DEB vs DES strategy in our study will help to provide insight into this question.

The noninferiority margin of 10% was high relative to the expected event rate of 12% or even the observed control group rate of 14.5%. The margin was selected on the basis of the historical performance of DES vs BA, the limited maximum of 20% BA in the control group, and a clinical benefit of reducing added stent layers. The clinician perspective of this benefit is demonstrated by reluctance to randomize

to DES for 2-layer ISR and with inclusion of 50% single-layer ISR in the group selected for BA control treatment. Although the difference between DEB and control treatment of 1.7% was consistent with expectations, an upper 95% credible interval lower than the observed 8.9% would have required a much larger trial. This would have been challenging on the basis of concerns for randomizing to DES in the current study.

STUDY LIMITATIONS. We excluded patients with >2 layers of previous stent, and the findings cannot be extrapolated to these patients. The results are limited to the specific study device and cannot be extrapolated to other drug-coated balloons. We used a blended control group to mirror practice in the United States at the time of study enrollment and before approval of a paclitaxel drug-coated balloon. This required limiting BA to 20% of the study group and resulted in lower enrollment of 2-layer ISR after BA randomization was closed. We included a relatively large noninferiority margin, and the results should be interpreted in the context of the preserved clinical benefit vs BA while avoiding additional layers of stent. The prespecified subgroups analyzed were underpowered to assess potential differences. Finally, outcomes are limited to 1 year and do not exclude potential differences emerging during longer-term follow-up.

CONCLUSIONS

In patients with ISR involving 1 or 2 previous BMS or DES layers, a novel sirolimus-eluting balloon was noninferior to a usual care strategy representing 80% DES and 20% BA, but it was not noninferior to DES for treatment of single-layer ISR. There was significant interaction on the basis of operator selection of DES vs BA.

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KEY WORDS coronary stent, drug-coated balloon, restenosis

APPENDIX For lists of the SELUTION4ISR Investigators, participating centers, study committees and laboratories, inclusion and exclusion criteria, and study endpoints, as well as supplemental tables and figures, please see the online version of this paper.