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ORIGINAL RESEARCH ARTICLE

Sirolimus-Eluting Balloon With Provisional Stenting Versus Systematic Drug-Eluting Stent Implantation to Treat De Novo Coronary Lesions: A Randomized, Open-Label, Noninferiority Trial

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BACKGROUND: Implantation of drug eluting stents (DESs) is currently the default approach for percutaneous coronary interventions, but long-term adverse events still exist. An approach with minimal stenting deserves to be assessed in a randomized trial. We studied a novel sirolimus-eluting balloon (SEB) that elutes sirolimus over a 90-day period using a biodegradable polymer microreservoir technology.

METHODS: In a multicenter, open-label, randomized trial, we compared an SEB-based strategy with provisional DES with one of systematic DES for de novo lesions in coronary arteries between 2 and 5 mm in diameter. Subjects were randomized 1:1 before percutaneous coronary intervention. The primary end point was target vessel failure, a composite of cardiac death, target vessel–related myocardial infarction, and clinically driven target vessel revascularization. It was tested for noninferiority at 1 year with the use of an absolute margin equal to 50% of the combined event rate at a significance level of 0.025. The primary analysis population included all randomized subjects with completed or attempted percutaneous revascularization, analyzed according to the intention-to-treat principle. A sensitivity analysis was performed on the per-protocol population.

RESULTS: Between August 27, 2021, and July 29, 2024, 3323 participants were randomized and treated in 62 sites. Among 1661 participants in the SEB strategy group, bailout stenting was performed in 343 (20.7%). Target vessel failure occurred over 365 days in 88 (5.3%) and 73 (4.4%) participants in the SEB and the systematic DES strategy groups, respectively (risk difference, 0.91% [95% CI −0.55% to 2.38%]; 1-sided *P*=0.02 for noninferiority with a 2.44% noninferiority margin). Clinically driven target vessel revascularization occurred more frequently in the SEB strategy group (3.3% versus 2.1%; risk difference, 1.22% [95% CI, 0.11%–2.33%). Safety events, including lesion thrombosis, were low and similar in both groups. Although the results of the per-protocol population (3194 participants, 96%) did not confirm noninferiority (upper boundary of the 95% CI, 2.63; *P*=0.04), they were similar to the intention-to-treat results in both magnitude and direction.

CONCLUSIONS: At 1 year, in the primary intention-to-treat analysis population, a strategy of percutaneous coronary intervention with SEB and provisional DES was noninferior to the systematic use of DES for the primary end point of target vessel failure. The per-protocol population sensitivity analysis did not confirm noninferiority. Clinically driven target vessel revascularization

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occurred more frequently in the SEB strategy group. At 5 years, target vessel failure will be tested again for noninferiority and for superiority if noninferiority is achieved.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: angioplasty ■ coronary artery disease ■ drug-eluting stents ■ percutaneous coronary intervention

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Clinical Perspective

What Is New?

- SELUTION DeNovo is the first large trial with clinical end points to show noninferiority at 1 year for the primary end point of target vessel failure of a strategy using sirolimus-eluting balloons (SEBs) with provisional stenting compared with systematic drug-eluting stent implantation for the treatment of de novo coronary lesions regardless of vessel size.
- In the SEB strategy group, 79.3% patients were treated with SEB only.
- The rates of cardiac death and myocardial infarction were low and similar at 1 year with both strategies, whereas the rate of target vessel revascularization was lower for the systematic drug-eluting stent strategy.

What Are the Clinical Implications?

- Early concerns about acute and subacute lesion thrombosis with a strategy of SEB and provisional stenting can be assuaged.
- For a large proportion of percutaneous coronary intervention candidates, an SEB-based strategy can safely be chosen over systematic stent implantation at the price of 1 additional target vessel revascularization for every 82 patients over the first follow-up year.
- Given the known clinical and cost-effectiveness of drug-eluting stents, the full efficacy, safety and cost benefit of a strategy using a SEB with a provisional drug-eluting stent will require further assessment after completion of the planned 5-year follow-up.

Nonstandard Abbreviations and Acronyms

BASKET SMALL 2	Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions
DCB	drug-coated balloon
DES	drug-eluting stent
FAS	full analysis set
ITT	intention to treat
MI	myocardial infarction
PCB	paclitaxel-coated balloon
PCI	percutaneous coronary intervention
PP	per-protocol
REC-CAGEFREE I	Paclitaxel-Coated Balloon for Treatment of De-Novo Non-Complex Coronary Artery Lesions
SEB	sirolimus-eluting balloon
TVF	target vessel failure
TVR	target vessel revascularization

The implantation of drug-eluting stents (DESs) is currently the default approach for percutaneous coronary interventions (PCI) but is associated beyond the first year with a 2% to 4% annual rate of adverse events, driven largely by neo-atherosclerosis and very late stent thrombosis.[1–4] Using drug-coated balloons (DCBs) together with minimal stenting could potentially deliver comparable early benefits while reducing the late DES attrition rate.

The use of paclitaxel-coated balloons (PCBs) has been evaluated mostly in small coronary de novo lesions or in-stent restenosis.[5–10] A recent large, randomized study of a PCB failed to achieve noninferiority compared with systematic DES implantation.[11] Several limus-coated balloons have been developed and compared with PCBs with mixed results.[12–14] The SELUTION SLR sirolimus-eluting balloon (SEB) with biodegradable polymer–based microreservoirs (MedAlliance LLC, a Cordis company, Irvine, CA) has shown encouraging early clinical results.[15] Drug retention on the SEB is high, and the elution profile is similar to currently available coronary DES (Supplemental Material).[16]

To evaluate the safety and efficacy of the SEB for treatment of coronary artery lesions by PCI, we designed a large, multicenter, open-label, randomized, noninferiority controlled trial with broad inclusion criteria, SELUTION DeNovo, comparing a SEB-based strategy with provisional DES with systematic DES implantation for patients with de novo coronary artery lesions.

METHODS

Study Design

The SELUTION DeNovo trial is conducted at 62 sites in 12 countries in Europe and Asia (Supplemental Material). It was registered on March 26, 2021, at http://www.clinicaltrials.gov (NCT04859985). The study design has previously been described, and the statistical analysis plan and the study protocol are available in the Supplemental Material.[17] The data that support the findings of this study are available from the corresponding author on reasonable request. Briefly, in a multicenter, open-label, randomized trial, we compared an SEB-based strategy with provisional DES with a systematic DES strategy for de novo coronary artery lesions between 2 and 5 mm in diameter. Subjects were randomized 1:1 before PCI. The primary end point, tested for noninferiority at 1 year, was target vessel failure (TVF), a composite of cardiac death, target vessel–related myocardial infarction (MI), and clinically driven target vessel revascularization (TVR).

The independent steering committee developed the trial protocol. Trial organization, data management, Clinical Event Committee and Data Safety Monitoring Board coordination, angiographic core laboratory, and statistical analysis (in collaboration with the Department of Public Health and Primary Care, KU Leuven, Belgium) were managed independently by the European Cardiovascular Research Center (Massy, France), an independent research organization contracted by the sponsor. Pseudonymized participant data were collected and stored in an electronic data capture system (Zelta platform by Merative LP, Ann Arbor, MI), which is US Food and Drug Administration 21 CFR Part 11 compliant. Angiograms were uploaded onto the decidemedical platform (ClinFlows, Bielefeld, Germany). Participant data were managed according to the European General Data Protection Regulation 2016/679. Data on sex and race were self-reported.

An independent Data Safety Monitoring Board regularly assessed the data to ensure participant safety, and an independent multidisciplinary Clinical Event Committee adjudicated all end point–related adverse events (Supplemental Material). The steering committee, fully blinded to accruing events in each arm, met on a weekly basis to review the first SEB cases from each center and all SEB cases requiring DES stenting to provide general feedback to the centers on the optimal use of SEB. Our trial is conducted in accordance with all applicable clinical trial regulations and guidelines, including the Declaration of Helsinki. Either the Institutional Review Board at each site or the National Ethics Committees approved the study. Signed written informed consent was provided by all participants before enrollment. The procedures followed were in accordance with institutional guidelines. The first 3 authors (C.S., F.K., K.B.) and last 2 authors (P.U., S.E.), constituting the steering committee, wrote the manuscript with full access to the data and vouch for the completeness and accuracy of data gathering and analysis, as well as for the fidelity of this report to the trial protocol. All authors approved the final manuscript.

Participants

The inclusion and exclusion criteria are listed in the Supplemental Material. In summary, participants were eligible if they had ≥1 native coronary lesions, all considered amenable to treatment with either SEB and provisional stenting or DES. Target vessel diameter was between 2 and 5 mm with TIMI (Thrombolysis in Myocardial Infarction) flow grade 2 or 3. The number of trial target lesions was not limited, but the investigators enrolled only participants whom they considered suitable for either strategy. The main exclusion criteria included ST-segment–elevation MI or non–ST-segment–elevation MI with ongoing chest pain or hemodynamic instability, previous PCI of a target vessel at any time, previous PCI of a nontarget vessel within 30 days or planned treatment of a left main lesion, arterial or venous graft, chronic total occlusion, or in-stent restenosis.

Randomization and Procedures

Participants were randomized 1:1 after angiography and before vessel preparation to the SEB or DES strategy with an interactive web-based system. Randomization sequences were generated before the first enrollment and remained concealed from all investigators. Participants in the SEB arm received lesion preparation according to the third DCB consensus (optimal balloon angioplasty with adjunct treatment using high-pressure balloon, lithotripsy, rotational atherectomy, or cutting or scoring balloon at the discretion of the operator when necessary).[18] After vessel preparation, 1 or several SEBs were inflated for a minimum of 30 seconds with a 1:1 balloon-to-vessel ratio. If at any stage (after lesion preparation or after use of SEB) stenting was considered necessary because of a persistent vessel threatening dissection, residual diameter stenosis >30%, or impaired coronary flow, 1 or several DESs could be implanted, and the participant remained in the SEB group. Participants randomized to the DES arm received treatment with DES as per local practice. In case of DES delivery failure, participants could be treated with any other device deemed appropriate, and they remained in the DES group. Intracoronary imaging was allowed in both trial arms but discouraged after the use of SEB to avoid displacing the sirolimus microreservoirs adhering to the treated vessel segment. Staged procedures with the initial treatment allocation for remaining target lesions were allowed if performed within 45 days after the index procedure. Angiograms were analyzed by an angiographic core laboratory (European Cardiovascular Research Center). Vessel size was defined according to the largest nominal diameter of the study device used.

Antiplatelet medication was prescribed before, during, and after the index procedure according to guidelines and hospital practice.[18,19] After discharge, subjects were followed up at 30 days and 6 and 12 months and will be followed up annually for 5 years.

Outcomes

The first primary end point is to demonstrate noninferiority at 1 year for TVF, a composite of cardiac death, target vessel–related MI, and clinically driven TVR. The second primary end point is noninferiority of the SEB strategy for TVF at 5 years. If noninferiority is achieved, a superiority test will be performed. Secondary end points include the components of the primary end point, all-cause mortality, stroke, bleeding, target lesion revascularization, and indices of procedural success.

Spontaneous MI was defined according to the fourth universal MI definition; periprocedural MI, lesion thrombosis and occlusive dissection, and clinically driven TVR were defined according to the Academic Research Consortium-2; bleeding

was defined according to the Bleeding Academic Research Consortium; and high bleeding risk was defined according to the Academic Research Consortium for High Bleeding Risk[20–24] (Supplemental Material). An independent clinical events committee adjudicated all end point–related events.

Statistical Analysis

The statistical analysis has been reported previously and is available in the Supplemental Material.[17] Briefly, to mitigate the risk of misspecifying the noninferiority margin at the design stage as a result of uncertainty in anticipated event rates, the absolute margin for the 1-year primary end point (TVF) was defined as 50% of the overall observed event rate for TVF. This approach avoids reliance on potentially inaccurate expected event rates and anchors the margin to the actual risk level in the trial population.[25] Assuming a 6% event rate and 2% dropout rate, 3260 subjects provided 95% power to demonstrate noninferiority with a margin equal to 50% of the combined event rate at a significance level of 0.025. Noninferiority is confirmed if the upper bound of the 2-sided 95% CI for the risk difference is below this margin. The expected event rates and noninferiority margins were determined according to clinical relevance and data from previous trials.[1,6]

TVF was analyzed with nonparametric cumulative incidence functions of the time to the first event, treating noncardiac death as a competing risk. Standard errors were determined with the delta method. The comparison between the 2 groups at 1 year was performed with a *Z* test. No formal comparison between the whole curves was performed. Subjects without an event were censored at their last known visit date. The primary analysis population is the full analysis set (FAS), including all randomized subjects with completed or attempted percutaneous revascularization, analyzed according to the intention-to-treat (ITT) principle. A per-protocol (PP) analysis excluding participants with major protocol violations was used for sensitivity analyses. The PP set was determined at a blinded review meeting before the 1-year analysis. Descriptive statistics for baseline and procedural characteristics are presented by treatment group. Secondary time-to-event end points were analyzed with Kaplan-Meier curves or cumulative incidence functions taking mortality as a competing risk. Given the exploratory nature of secondary end points, only 95% CIs without adjustment for multiplicity are reported and should not be used to infer definitive treatment effects. Data were analyzed with SAS/STAT software version 15.2.

Role of the Funding Source

The trial was funded by Cordis through its affiliate MA Med Alliance SA, Nyon, Switzerland. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Participants

Between August 27, 2021, and July 29, 2024, 3341 participants across 62 sites from 12 countries were randomized. The primary analysis is based on the FAS of 3323 subjects, after the exclusion of 1 patient who withdrew consent, 2 for whom exclusion criteria were noted before PCI, and 15 who had no PCI procedure. Consequently, 1661 participants in the SEB with provisional stenting strategy group and 1662 in the systematic DES strategy group were analyzed. Follow-up at 365 days (or until death) was completed for 3260 participants (98.1%; Figure 1). Baseline characteristics were well balanced between groups (Table 1). Higher-risk subjects included those with acute coronary syndrome (32.6%) and those

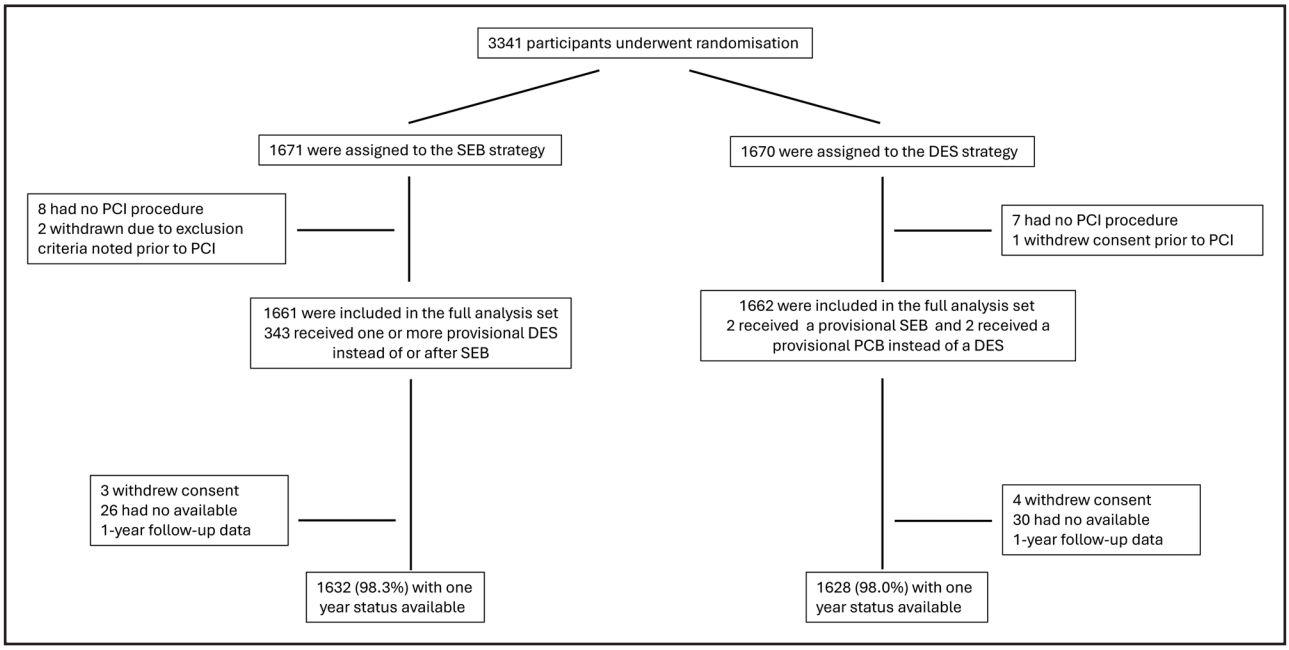

Figure 1. Trial profile.
DES indicates drug-eluting stent; PCI, percutaneous coronary intervention; SEB, sirolimus-eluting balloon; and PCB, paclitaxel-eluting balloon.

Table 1. Clinical, Angiographic, and Procedural Characteristics

	SEB strategy	DES strategy
Patient characteristics		
Patients, n	1661	1662
Age, y	67.1±9.7	66.7±10.4
Female sex, n (%)	410 (24.7)	432 (26.0)
Body mass index, kg/m^2	28.3±4.9, n=1605	28.3±5.0, n=1611
Medical history, n (%)		
Diabetes	425 (25.6)	434 (26.1)
Insulin-dependent diabetes	82 (4.9)	94 (5.7)
Hypertension	1151 (69.3)	1168 (70.3)
Hypercholesterolemia	1093 (65.8)	1075 (64.7)
Prior MI	303 (18.2)	294 (17.7)
Prior stroke	69 (4.2)	73 (4.4)
Previous PCI	456 (27.5)	451 (27.1)
Previous CABG	37 (2.2)	44 (2.6)
Current smoker	297 (17.9)	326 (19.6)
Renal failure (GFR <60 mL/min)	82 (4.9)	79 (4.8)
Congestive heart failure	89 (5.4)	80 (4.8)
High bleeding risk	269/1513 (17.8)	253/1551 (16.3)
Atrial fibrillation on baseline ECG	85 (5.1)	77 (4.6)
Acute coronary syndrome	553 (33.3)	529 (31.8)
Chronic coronary syndrome	1108 (66.7)	1133 (68.2)
Angiographic characteristics		
Treated lesions, n	2243	2264
Treated lesions per patient, n	1.4±0.6	1.4±0.7
Treated vessels per patient, n	1.2±0.4	1.2±0.4
Patients with multivessel procedure(s), n (%)	263 (15.8)	284 (17.1)
Location of treated lesions		
Left main	3 (0.1)	7 (0.3)
Left anterior descending artery	1069 (47.7)	1070 (47.3)
Proximal left anterior descending artery	404 (18.0)	437 (19.3)
Left circumflex artery	600 (26.7)	598 (26.4)
Right coronary artery	575 (25.6)	595 (26.3)
Vessel size ≥3.0 mm*	1494/2221 (67.3)	1399/2206 (63.4)
Bifurcation lesion†	676/2107 (32.1)	646/2100 (30.8)
Moderate or heavy calcified lesion†	520/2108 (24.7)	471/2106 (22.4)
ACC/AHA type B2 or C lesion†	1406/2104 (66.8)	1310/2103 (62.3)
Procedural characteristics		
Procedures, n (%)	1783	1776
Single procedure, n (%)	1543 (92.9)	1551 (93.3)
Staged procedure, n (%)	118 (7.1)	111 (6.7)
Radial access, n (%)	1664 (93.3)	1677 (94.4)
Lesion preparation, n (%)	2243 (100)	1902 (84)
Speciality balloon use per lesion, n (%)‡	639 (28.5)	178 (7.9)
Rotational atherectomy or IVL use per lesion, n (%)	81 (3.6)	57 (2.5)
Intracoronary imaging use per lesion, n (%)§	333/2019 (15.8)	397/2113 (18.8)
No. of SEB or DES used per lesion	1.3±0.6	1.2±0.5)

(*Continued*)

Table 1. Continued

	SEB strategy	DES strategy
No. of SEB or DES used per patient	1.7±1.0	1.6±0.9
Nominal diameter of SEB or DES per device, mm	3.1±0.5, n=2221	3.1±0.5, n=2206
Mean inflation duration for SEB per device, s	62.1±28.9, n=2304	NA
Total length of SEB or DES per lesion, mm	31.6±17.1, n=2221	28.7±15.1, n=2206
Bail-out DES or DCB per lesion, n (%)	405 (18.1)	4 (0.2)‖
After lesion preparation (no SEB used), n (%)	250 (11.1)	NA
After SEB used, n (%)	155 (6.9)	NA
Procedural duration, min	55±32	53±35

Data are number (percent), mean (SD), or number/total (percent). Patient, lesion, and device numbers are shown if group size was different from the total in each group.

ACC/AHA indicates American College of Cardiology/American Heart Association; CABG, coronary artery bypass grafting; DCB, drug-coated balloon; DES, drug-eluting stent; GFR, glomerular filtration rate; IVL, intravascular lithotripsy; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; and SEB, sirolimus-eluting balloon.

High bleeding risk is defined as a high bleeding risk score ≥1 according to the Academic Research Consortium high bleeding risk.[23]

*Vessel size is defined according to the largest nominal diameter of the device (SEB or DES) used.

†Based on a qualitative analysis of available angiograms by the core laboratory.

‡Specialty balloons include scoring, cutting, and very high-pressure ballons.

§Intracoronary imaging includes intravascular ultrasound and optical coherence tomography.

‖Two SEBs and 2 other DCBs.

at high risk for bleeding (17.0%). A total of 4507 lesions were treated in 3323 participants (1.4±0.7 lesions per participant on average); 18.7% lesions were in the proximal left anterior descending artery. Lesion complexity was represented by 23.5% having moderate or severe calcification, 31.4% were bifurcation lesions, and 64.6% were type B2 or C according to the modified American College of Cardiology/American Heart Association classification. The largest nominal diameter of SEB or DES used was ≥3.0 mm for 65.3% of lesions.

Before study device use, lesion preparation was performed in all lesions in the SEB strategy group and in 84% in the DES strategy group. In the SEB strategy group, stenting was performed in 18.1% of lesions. Reasons for stenting included threatening dissection (10.7%), poor flow (1.7%), and residual stenosis (6.0%). At 30 days and 6 and 12 months, dual antiplatelet therapy was taken by 81.5%, 60.2%, and 27.5% of participants, respectively, in the SEB arm and 89.5%, 70.1%, and 29.6% participants in the DES arm (Table S4).

Outcomes

The overall 1-year TVF rate across the entire study population was 4.88%, which established the prespecified noninferiority margin at 2.44% (50% of the observed rate). In the FAS population (n=3323), the 1-year TVF rate was 5.3% (88/1661) in the SEB strategy group versus 4.4% (73/1662) in the systematic DES group. The risk difference was 0.91% (95% CI, −0.55% to 2.38%; $P_{\text{noninferiority}}$=0.02). Because the upper bound of the 95% CI (2.38%) was below the 2.44% margin, noninferiority of the SEB-based strategy was demonstrated (Figures 2 and 3 and Table 2). Clinically driven TVR, a component

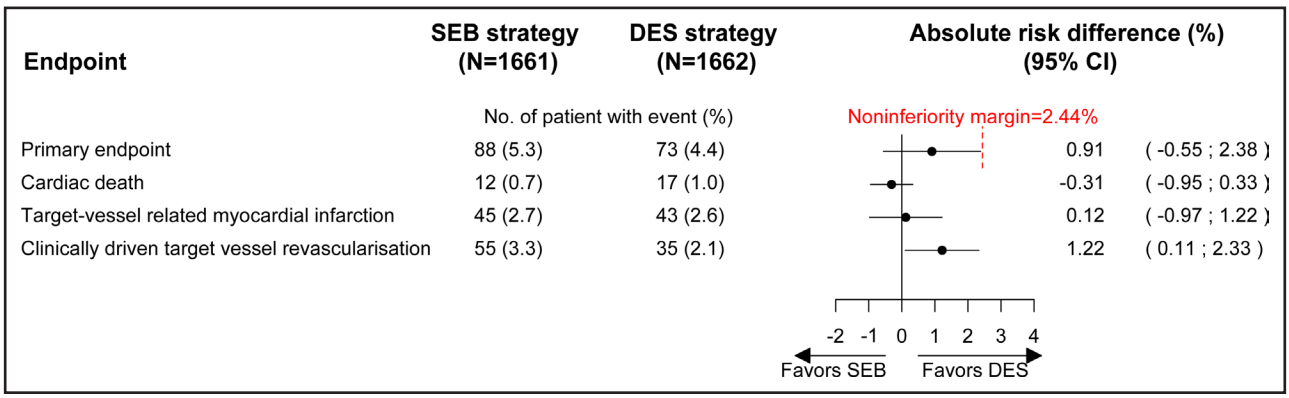

Figure 2. Primary end point and its components.

Primary end point was target vessel failure, a composite of cardiac death, target vessel–related myocardial infarction, and clinically driven target vessel revascularization. Percentages are determined from a cumulative incidence curve taking (all or noncardiac) mortality into account as a competing risk.

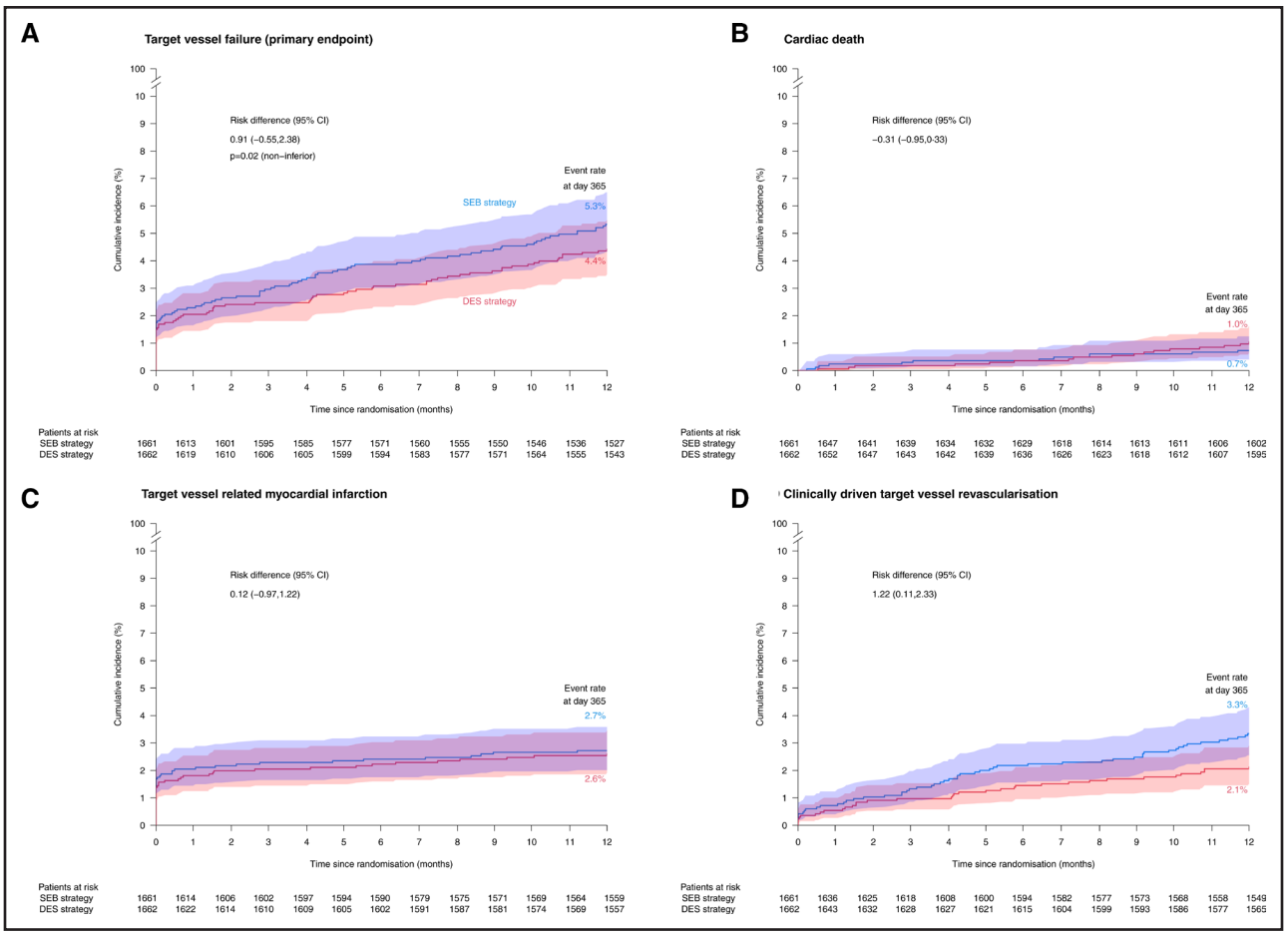

Figure 3. Cumulative incidence curves for the primary end point and its components.
Primary end point was target vessel failure a composite of cardiac death, target vessel–related myocardial infarction, and clinically driven target vessel revascularization. Colored bands are 95% pointwise confidence bands. Noninferiority margin was 2.44%.

of the primary end point, occurred more frequently in the SEB strategy group (3.3% versus 2.1%; risk difference, 1.22% [95% CI, 0.11%–2.33%]). TVF of patients treated with SEB only was 5.0% (65/1310; Table S5).

In the PP population (n=3194), the 1-year TVF rate was 5.2% in the SEB strategy group versus 4.1% in the systematic DES group. The risk difference was 1.09% (95% CI, −0.45% to 2.63%; $P_{\text{noninferiority}}$=0.04). Because the upper bound of the 95% CI (2.63%) exceeded the 2.44% margin, noninferiority was not confirmed, although the results were similar to the ITT in both magnitude and direction. The likelihood of protocol deviations increased with procedure complexity. The 129 patients excluded from the PP analysis had more complex lesions, more multilesion and multivessel procedures, and accordingly higher rates of adverse events. The effect was more pronounced in the DES arm (Table S7 and Figure S1).

Secondary end points are reported in Table 2. Interaction testing of predefined participant subsets suggested heterogeneity of treatment effect for TVF favoring the use of DES in women (TVF in the SEB strategy group 7.4% versus 3.7% in the DES strategy group; $P_{\text{interaction}}$=0.04) and in favor of SEB in participants with at least 1 moderately or heavily calcified lesion (*P*=0.01) and those at high bleeding risk (*P*=0.04). There was no interaction in patients with bifurcations (*P*=0.57) or those with multivessel procedures (*P*=0.10; Figure 4).

The rate of patients receiving dual antiplatelet therapy at 1 and 6 months was significantly higher in the DES strategy group (Table S4). This did not translate into differences in lesion thrombosis, MI, or bleeding complications.

DISCUSSION

SELUTION DeNovo is the first trial with clinical end points at 1-year follow-up to show that a strategy of PCI with SEB and provisional DES is noninferior to a strategy of PCI with systematic DES for participants with de novo coronary lesions of all sizes.

Our study supports the safety of SEB in patients undergoing de novo PCI. Rates of acute and subacute lesion thrombosis were low and comparable in both arms (0.5% versus 0.4% in the SEB and DES arms, respectively), and rates of cardiovascular death and MI at 30 and 365 days were similar in the 2 groups (Table 2 and

Table 2. Primary and Secondary End Points at 1 Year

	SEB strategy (n=1661), n (%)*	DES strategy (n=1662), n (%)*	Risk difference (95% CI), %†
Primary end point (composite of cardiac death, target-vessel–related MI and clinically driven TVR)	88 (5.3)	73 (4.4)	0.91 (−0.55, 2.38)‡
Cardiac death	12 (0.7)	17 (1.0)	−0.31 (−0.95, 0.33)
Target vessel–related MI	45 (2.7)	43 (2.6)	0.12 (−0.97, 1.22)
Clinically driven TVR	55 (3.3)	35 (2.1)	1.22 (0.11, 2.33)
All-cause death	30 (1.8)	34 (2.1)	−0.25 (−1.19, 0.70)
Stroke	8 (0.5)	5 (0.3)	0.18 (−0.25, 0.61)
Any MI	53 (3.2)	53 (3.2)	0.0 (−1.20 1.20)
Periprocedural MI	30 (1.8)	27 (1.6)	0.18 (−0.70, 1.06)
Lesion thrombosis	9 (0.5)	12 (0.7)	−0.18 (−0.72, 0.36)
Acute	7 (0.4)	5 (0.3)	0.12 (−0.29, 0.53)
Subacute	1 (0.1)	2 (0.1)	−0.06 (−0.27, 0.14)
Late	2 (0.1)	5 (0.3)	−0.18 (−0.50, 0.13)
Definite	9 (0.5)	11 (0.7)	−0.12 (−0.65, 0.41)
Probable	1 (0.1)	1 (0.1)	0.00 (−0.17, 0.17)
BARC 3–5 bleeding	20 (1.2)	22 (1.3)	−0.12 (−0.88, 0.65)
Any TVR	63 (3.8)	38 (2.3)	1.52 (0.35, 2.70)
Any TLR	56 (3.4)	34 (2.0)	1.34 (0.23, 2.45)
Clinically driven TLR	49 (3.0)	29 (1.8)	1.22 (0.18, 2.25)
Any revascularization	90 (5.5)	62 (3.8)	1.71 (0.27, 3.14)
New lesion revascularization in a target vessel	8 (0.5)	7 (0.4)	0.06 (−0.40, 0.52)
Non-TVR	34 (2.1)	27 (1.6)	0.43 (−0.49,1.35)
Device success§	1954 (84.5)	2426 (93.4)	−8.9 (−11.1, −6.7)
Device success when SEB only is used§	1830 (92.0)	NA	NA
Lesion success‖	2107 (93.9)	2222 (98.1)	−4.2 (−5.4, −3.0)
Procedure success‖	1624 (91.1)	1707 (96.1)	−5.0 (−6.6, −3.4)

Data are number (cumulative event rate) or difference (95% CI).

BARC indicates Bleeding Academic Research Consortium; DES, drug-eluting stent; MI, myocardial infarction; NA, not applicable; SEB, sirolimus-eluting balloon; TLR, target lesion revascularization; and TVR, target vessel revascularization.

*Percentages are determined from a cumulative incidence curve taking (all or noncardiac) mortality into account as a competing risk except for all-cause mortality, for which a Kaplan-Meier curve is used.

†The widths of the CIs have not been adjusted for multiplicity and should not be used to infer definitive treatment effects with the exception for the primary end point.

‡Noninferiority shown using a noninferiority margin of 2.44%; 1-sided noninferiority P=0.02 to be evaluated at 0.025.

§Device success is defined as achievement of a final residual diameter stenosis of <30% (site reported) using the assigned device only (numerator and denominator are study devices). Use of DES after SEB is counted as a device failure. The denominators are 2312 and 2597 for the SEB and DES strategy, respectively. The denominator in the SEB strategy is 1990 when SEB only is used.

‖Lesion success is defined as achievement of <30% residual stenosis (site-reported) using any percutaneous method. Numerator and denominator are study lesions. The denominators are 2243 and 2264 for the SEB and DES strategy, respectively.

‖Procedure success defined as achievement of a final diameter stenosis of <30% (site reported) in all target lesions using any percutaneous coronary intervention method, without the occurrence of death, MI, or repeat TVR during hospital stay. Numerator and denominator are study procedures (index and staged combined). The denominators are 1783 and 1776 for the SEB and DES strategy, respectively.

Table S3). Although SEB was noninferior to DES with respect to TVF, clinically driven TVR occurred in 3.3% and 2.1% of participants in the SEB and DES strategy arms, respectively, and several secondary end points (any revascularization, any TVR; Table 2) documented a greater need for repeat revascularization for the SEB than for the DES strategy at 1 year. Nevertheless, we were able to avoid stent use in nearly 80% of patients in the SEB group. Potential early advantages of not implanting a stent include easier access to side branches, lesser dependence on dual antiplatelet duration, and simplified treatment of potential restenosis. Later, vasomotion and positive remodeling are preserved, and adverse events such as stent fracture, chronic stent recoil, neo-atheroma, and very late thrombosis are avoided.[1,2] The full benefits of a strategy with minimal stenting could therefore gradually become apparent over the years. We plan to obtain 5-year follow-up to assess whether the 1-year conclusions hold over time. If noninferiority is maintained, a superiority test will be applied.

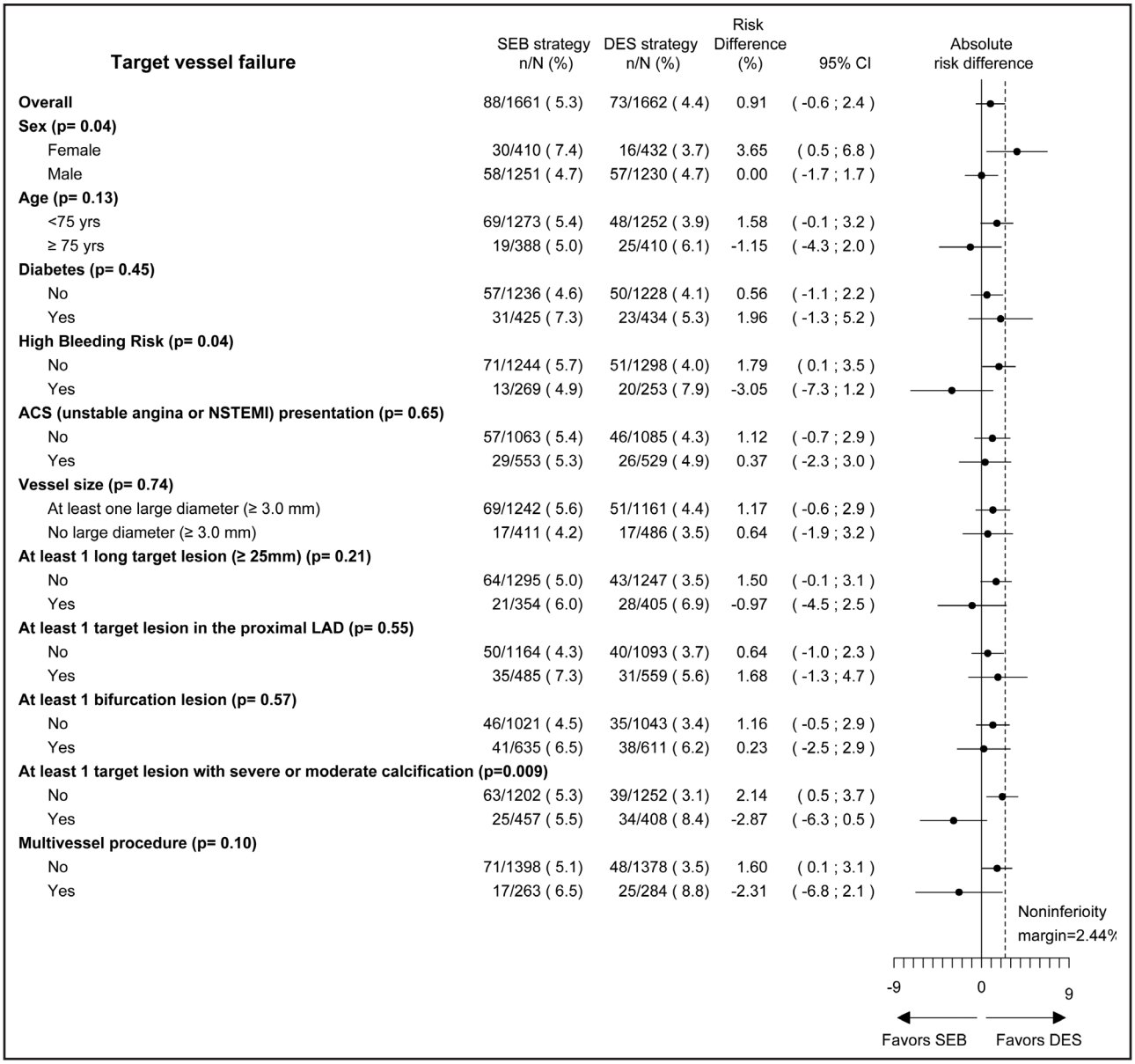

Figure 4. Subgroup analyses.

Shown are the rates of the primary end-point target vessel failure, a composite of cardiac death, target vessel–related myocardial infarction, and target vessel clinically driven revascularization, at 1 year. *P* value in parentheses behind the subgroup label is the test for interaction. Risk difference displays the sirolimus-eluting balloon (SEB) minus the drug-eluting stent (DES) rate. High bleeding risk is a high bleeding risk score >1 according to the Academic Research Consortium high bleeding risk. Vessel size was defined according to the largest nominal diameter of the study device used. ACS indicates acute coronary syndrome; LAD, left anterior descending coronary artery; and NSTEMI, non–ST-segment–elevation myocardial infarction.

It is important to note that although noninferiority was established in the prespecified primary analysis in the FAS, the PP sensitivity analysis did not meet the noninferiority criterion. The ITT principle was chosen for the primary analysis because it appeared better suited to compare 2 strategies by eliminating selection bias and minimizing confounding factors. It will allow a potential superiority analysis on the same fully randomized population at 5 years. Given the consistent results, the smaller effective sample size of the PP population, and the potential for imbalance once randomization is no longer preserved, this finding can be interpreted as reflecting reduced precision rather than a substantive difference in treatment effect (Figure S1).[25]

Interaction testing of predefined participant subsets suggested heterogeneity of treatment effect in favor of SEB in participants with at least 1 moderately or heavily calcified lesion and those at high bleeding risk, both groups of participants known to carry an increased ischemic and thrombotic risk (Figure 4).[26,27] Calcification was defined by the core laboratory on the basis of angiography, not by intravascular ultrasound or optical coherence

tomography. A recent meta-analysis of DCB and DES outcomes in the setting of calcification showed comparable results between the 2 devices.[28] Underexpansion of DES in calcified lesions has been suggested as a cause of adverse events, emphasizing the importance of lesion preparation before stent implantation.[29]

Interaction testing also suggested heterogeneity, with results favoring DES in female patients. Despite often having smaller vessels and more diffuse lesions, women tend to be treated for less complex lesions, possibly as a result of a selection bias.[30] There was no significant interaction of vessel size, presence of bifurcations, or multivessel procedures. No correction for multiple testing was applied to the subgroup analyses, which should be interpreted with caution and are to be seen as hypothesis generating only.

Previous trials comparing PCBs with DES for de novo lesions randomized participants only after successful lesion predilatation, thus comparing devices and not strategies, and therefore reported comparatively low rates of bailout DES after PCB use (5.1% for BASKET SMALL 2 [Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions] and 9.4% for REC-CAGEFREE I [Paclitaxel-Coated Balloon for Treatment of De-Novo Non-Complex Coronary Artery Lesions]).[6,11] Our trial design was different, being strategy based with randomization before lesion preparation and broad inclusion criteria and including 16.5% of participants with multivessel procedures. Stenting in our study was used instead of SEB for 11.1% of lesions after lesion preparation and in 6.9% of lesions after SEB use. Stenting was thus part of the SEB strategy, but 79.3% of participants and 81.9% of lesions could be treated with SEB alone. TVF of patients treated with SEB only was 5.0% (65/1310), but this number should be interpreted with caution because this analysis was not prespecified and represents patients who responded well to lesion preparation (Table S5). BASKET SMALL 2 selected 758 participants with target vessels <3.0 mm in diameter and found that a PCB was noninferior to first- and second-generation DES. REC-CAGEFREE I enrolled 2272 participants with noncomplex de novo lesions of all sizes to compare a PCB with a sirolimus DES with a 2-year follow-up. The trial failed to show noninferiority for a composite of cardiovascular death, target vessel–related MI, and target lesion revascularization.

Smaller trials with angiographic end points assessing other limus-coated balloons and PCBs have yielded conflicting results, and larger trials with clinical end points are ongoing.[31]

The majority of currently available DCBs are coated with paclitaxel. Paclitaxel is highly lipophilic, which facilitates efficient coating onto balloon surfaces and rapid transfer into the vessel wall during a brief balloon inflation, with prolonged tissue retention due to strong intracellular binding. Consequently, PCBs are characterized by high initial tissue concentrations and durable retention. In contrast, sirolimus is less lipophilic and therefore requires dedicated carrier technologies to enable effective vascular uptake and sustained release. Several techniques have been developed. The SELUTION SLR SEB is coated with a phospholipid blend and sirolimus is encapsulated with a biodegradable polymer in microreservoirs. This allows controlled, extended elution with prolonged drug availability, mimicking the kinetics of limus-eluting stents (Supplemental Material).[16] These differences are further reflected in pharmacological profiles: Paclitaxel acts as a cytotoxic agent with sustained tissue persistence, whereas sirolimus is cytostatic with a shorter tissue half-life and wider therapeutic window.[32] Randomized studies comparing DCBs are necessary to determine whether variations in drugs and carrier technologies translate into different clinical outcomes.

Cost differences between the 2 strategies were not evaluated in our study. In the BASKET-SMALL 2 study, DCB was less cost-effective than DES at 3 years in the treatment of small vessel coronary artery disease, although results varied substantially when uncertainty was accounted for in model parameters.[33] In a retrospective analysis from a large cohort of cases in an established DCB center, the cost-effectiveness of DCB-only angioplasty was compared with DES angioplasty. Per-patient and per-lesion results were not different.[34]

Device, procedure, and lesion success was lower in the SEB strategy arm (Table S7). We used definitions based on guidelines for DES. In both groups, success was based on achievement of a site-reported final diameter stenosis of <30%. For DCB, this is a more stringent criterion than the current 2025 guidelines, which recommend achieving a residual stenosis of <40%.[35]

Our trial has limitations. The inclusion criteria were broad but excluded participants with ST-segment–elevation MI and those with chronic total occlusion or left main stenosis. These more complex and higher-risk groups will require further evaluation when the early learning curve for DCB use is overcome. Another high-event-rate group that was excluded was patients with in-stent restenosis in whom the benefits of the SELUTION SLR have been assessed in the SELUTION4ISR trial.[36] The protocol did not require systematic biomarker determination after the procedures, and the incidence of periprocedural MI may have been underestimated but still represents 54% of all-target-vessel related MI. Antithrombotic regimens were not protocol defined, and differences were noted between groups, which could have influenced the primary outcome. At the beginning of the trial, many participating centers had limited experience with the use of DCB for de novo lesions; therefore, a learning curve effect may have influenced the results in the SEB strategy arm. The use of specialty balloons, calcification modification techniques, and intracoronary imaging was limited. This may have affected outcomes in both groups,

but it reflects current clinical practice in the participating centers. Lesion preparation was not mandatory in the DES strategy arm, which may have negatively influenced the results of that group.

Several methodological limitations deserve to be mentioned. Our trial compared 2 strategies and does not allow direct comparison between SEB and DES. The observed control rate (4.4%) was lower than assumed; therefore, testing at 1 year had less power than anticipated. Noninferiority margins are always debatable, and ours may be considered liberal. Our choice was based on clinical relevance and data from previously published trials but limited by the paucity of data on DCBs in de novo lesions when the trial was designed.[1,2,6,8] We defined our margin for the 1-year primary end point (TVF) as 50% of the overall observed event rate for the 1-year primary end point (TVF). This approach avoids reliance on a potentially inaccurate expected rate and anchors the margin to the actual risk level of the trial population. Under the assumption that no difference was expected between the 2 treatment groups (as also assumed in the sample size calculation), the overall rate was seen as an appropriate estimate of the true control rate. Using the observed rate might increase the type I error, but post hoc simulations have confirmed that this increase is very limited up to the lower limit of the 95% CI of the control rate, and our result remains valid when tested at a lower level of significance, that is, 0.023, which limits the type I error to 2.5%. We believe that the 2.44% margin itself is reasonable and below the rates observed in a majority of published stent versus stent noninferiority trials.[37,38] As planned, noninferiority was established in the FAS according to the ITT principle.[17] This conclusion must be tempered by the fact that noninferiority was not reached in the PP population. Last, assessing the full benefit of a minimal stenting strategy requires longer follow-up. This is ongoing, and a second hierarchical noninferiority primary end point will be assessed at 5 years. If positive, superiority testing will be performed.

CONCLUSIONS

This large trial, which randomized 3323 participants to undergo either PCI with SEB and a provisional DES or PCI with systematic use of DES, met the predefined noninferiority criterion at 1 year in the primary analysis population using the ITT principle. In the PP population, noninferiority was not confirmed, although the results were numerically consistent with the primary analysis. Clinically driven TVR occurred more frequently in the SEB strategy group. At 5 years, TVF will be tested again for noninferiority and for superiority if noninferiority is established.

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Supplemental Material

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Enrollment inclusion and exclusion criteria
Study device
End-point definitions
Tables S1–S7
Figure S1
Study protocol
Statistical analysis plan

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