JACC: CARDIOVASCULAR INTERVENTIONS VOL. 12, NO. 6, 2019

PUBLISHED BY ELSEVIER

Treatment of Coronary Drug-Eluting Stent Restenosis by a Sirolimus- or Paclitaxel-Coated Balloon

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ABSTRACT

OBJECTIVES The aim of this randomized controlled trial was to investigate a novel sirolimus-coated balloon (SCB) compared with the best investigated paclitaxel-coated balloon (PCB).

BACKGROUND Treatment of coronary in-stent restenosis (ISR) remains challenging. PCBs are an established treatment option outside the United States with a Class I, Level of Evidence: A recommendation in the European guidelines. However, their efficacy is better in bare-metal stent (BMS) ISR compared with drug-eluting stent (DES) ISR.

METHODS Fifty patients with DES ISR were enrolled in a randomized, multicenter trial to compare a novel SCB (SeQuent SCB, 4 μg/mm^2) with a clinically proven PCB (SeQuent Please Neo, 3 μg/mm^2) in coronary DES ISR. The primary endpoint was angiographic late lumen loss at 6 months. Secondary endpoints included procedural success, major adverse cardiovascular events, and individual clinical endpoints such as stent thrombosis, cardiac death, target lesion myocardial infarction, clinically driven target lesion revascularization, and binary restenosis.

RESULTS Quantitative coronary angiography revealed no differences in baseline parameters. After 6 months, in-segment late lumen loss was 0.21 ± 0.54 mm in the PCB group versus 0.17 ± 0.55 mm in the SCB group (p = NS; per-protocol analysis). Clinical events up to 12 months also did not differ between the groups.

CONCLUSIONS This first-in-man comparison of a novel SCB with a crystalline coating shows similar angiographic outcomes in the treatment of coronary DES ISR compared with a clinically proven PCB. (Treatment of Coronary In-Stent Restenosis by a Sirolimus [Rapamycin] Coated Balloon or a Paclitaxel Coated Balloon [FIM LIMUS DCB]; NCT02996318) (J Am Coll Cardiol Intv 2019;12:558-66) © 2019 by the American College of Cardiology Foundation.

Restenosis after coronary stent implantation remains a clinically relevant scenario, even in the era of newer-generation drug-eluting stents (DES). The occurrence of in-stent restenosis (ISR) is associated with worsened clinical outcomes (1). Two endovascular treatment options for ISR have been identified as clinically relevant: the implantation of another DES or the use of a drug-coated balloon (DCB) (2), both with a Class I, Level of Evidence: A recommendation in the 2018 European guidelines for revascularization (3). Even small randomized trials showed superiority of paclitaxel-coated balloons (PCBs) over conventional angioplasty in bare-metal stent (BMS) ISR (4) and DES ISR (5). Compared with first-generation DES, DCB treatment of ISR was similar in angiographic outcomes (6-8) and superior in hard clinical endpoints on longer-term follow-up (9,10). However, as other

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Manuscript received September 17, 2018; revised manuscript received November 18, 2018, accepted November 27, 2018.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.11.040

endovascular treatments PCBs are associated with higher event rates in the case of DES ISR compared with BMS ISR (11). Furthermore, angiographic and clinical outcomes depend on a variety of variables including the quality of lesion preparation during the index procedure (12,13), resulting in conflicting results in randomized clinical trials comparing current-generation DES with PCBs (14–17) and make it difficult to draw final conclusions from registries. The clinical outcome appears to be comparable with PCBs and second-generation DES. The advantage of DES is a larger minimal lumen diameter post-procedure and the advantage of the PCB is avoiding a second stent layer.

Limus-eluting stents are dominating coronary interventions, although paclitaxel is the only drug on balloon catheters with proven inhibition of restenosis. So far, paclitaxel is the preferred drug for balloon coating due to its irreversible binding to the microtubes (18) resulting in long persistence in the vascular cells (19,20) and favorable cell-specific effects (21). Sirolimus and its analogs reversibly bind to FKBP 12, forming a complex with the mammalian target of rapamycin, thus blocking cell cycle progression at the juncture of the G1 and S phases (22). In the case of local drug delivery by stents, sirolimus must be released for a period of several weeks for effective inhibition of neointimal proliferation (23).

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Balloon-based delivery of sirolimus should include some form of delayed-release technology to overcome this reversible binding on the mammalian target of rapamycin. Few studies indicated neointimal inhibition by limus-coated balloons in animals (24), especially for zotarolimus (25,26). Different sirolimus coatings on balloons showed a rapid decrease of tissue concentrations when applied by balloons (27,28). In contrast, a crystalline sirolimus coating with BHT (butylated hydroxytoluene) as excipient was associated with persistent vessel concentrations of up to 50% of the initial concentration at 1 month (29).

The aim of this first randomized controlled multicenter clinical trial was to investigate a novel coated balloon using a crystalline sirolimus coating with a dose of 4 μg/mm^2 (SCB) in patients with DES ISR first and foremost to exclude a major inferiority versus highly efficacious PCB.

METHODS

STUDY DESIGN AND PATIENT POPULATION. Fifty patients were enrolled in a randomized, prospective, controlled multicenter trial investigating the efficacy and safety of a SCB (sirolimus-coated SeQuent Neo percutaneous transluminal coronary angioplasty balloon catheter; B. Braun Melsungen, AG Vascular Systems, Berlin, Germany; coated with sirolimus 4 μg/mm^2 balloon surface by InnoRa GmbH, Berlin, Germany) compared with a commercially available PCB (SeQuent Please Neo 3 μg/mm^2 balloon surface, B. Braun Melsungen). The study was conducted at 5 departments of cardiology in Malaysia (National Heart Institute, Kuala Lumpur; University Malaya Medical Centre, Kuala Lumpur; Queen Elizabeth Hospital II, Kota Kinabalu; Sarawak Heart Centre, Kota Samarahan; Penang General Hospital, Penang). Study coordination, data management, on-site monitoring, and financial support were provided by InnoRa GmbH. The study sponsor did not have any role in analysis and interpretation of data or writing of the manuscript and did not participate in the decision to submit the manuscript for publication. Study devices were provided by B. Braun Melsungen. The study was performed according to the Declaration of Helsinki and World Health Organization guidelines. All patients gave written informed consent. The local ethical committees approved the study.

Patients at least 18 years of age with clinical evidence of stable or unstable angina or a positive functional study and up to 2 restenotic lesions in a stented coronary artery with DES were considered for enrollment. Major clinical exclusion criteria were ST-segment elevation myocardial infarction within the past 72 h; chronic renal insufficiency with serum creatinine levels >2.0 mg/dl; known hypersensitivity or contraindications to aspirin, heparin, clopidogrel, ticlopidine, paclitaxel, or sirolimus; sensitivity to contrast media not amenable to pre-medication; lesion length >35 mm; or vessel diameter <2.5 mm. Cardiac catheterization and intervention was carried out according to hospital practice.

After assessment for angiographic and clinical inclusion and exclusion criteria, patients were randomly assigned on a center-by-center basis by closed envelops to undergo balloon angioplasty of the target lesion with either a PCB or a SCB catheter. Predilatation of the target lesion was mandatory, using a nonstudy uncoated balloon catheter with a diameter 0.5-mm smaller than or similar to the size of the reference vessel diameter or the diameter of the previously implanted restenotic stent. The recommended study DCB balloon inflation time was 30 to 60 s at nominal pressure. The patients were preloaded with $P2Y_{12}$-antagonist and on aspirin before coronary angioplasty. Unfractionated heparin was

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)
DCB = drug-coated balloon
DES = drug-eluting stent(s)
ISR = in-stent restenosis
LLL = late lumen loss
MACE = major adverse cardiovascular event(s)
PCB = paclitaxel-coated balloon
SCB = sirolimus-coated balloon

TABLE 1 Clinical Baseline Data

	PCB (n = 25)	SCB (n = 25)	p Value
Age, yrs	58.6 ± 12.5	61.6 ± 11.7	0.393
Male	19/25 (76)	22/25 (88)	0.464
Height (cm)	164.0 ± 7.0	166.2 ± 7.9	0.310
Weight (kg)	79.3 ± 23.8	73.4 ± 12.2	0.279
Angina pectoris status stable	15/25 (60)	13/25 (52)	0.776
CCS class			
I	10/25 (40)	8/25 (32)	0.561
II	14/25 (56)	17/25 (68)	
IV	1/25 (4)	0/25 (0)	
Prior CABG	4/25 (16)	1/25 (4)	0.975
History of any myocardial infarction	9/25 (36)	8/25 (32)	>0.99
Hypertension	23/25 (92)	24/25 (96)	0.490
Prior stroke	1/25 (4)	0/25 (0)	0.490
Diabetes	19/25 (76)	18/25 (72)	>0.99
Insulin	6/19 (32)	7/18 (39)	0.737
Hyperlipidemia	21/25 (84)	23/25 (92)	0.667
Smoking	2/25 (8)	4/25 (16)	0.423

Values are mean ± SD or n/N (%).

CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; PCB = paclitaxel-coated balloon; SCB = sirolimus-coated balloon.

given according to the standard hospital practice and activated clotting time was kept above 250 s. Most of the procedure was performed via radial access. Vascular sheaths either through transradial or transfemoral route were removed according to usual hospital practice.

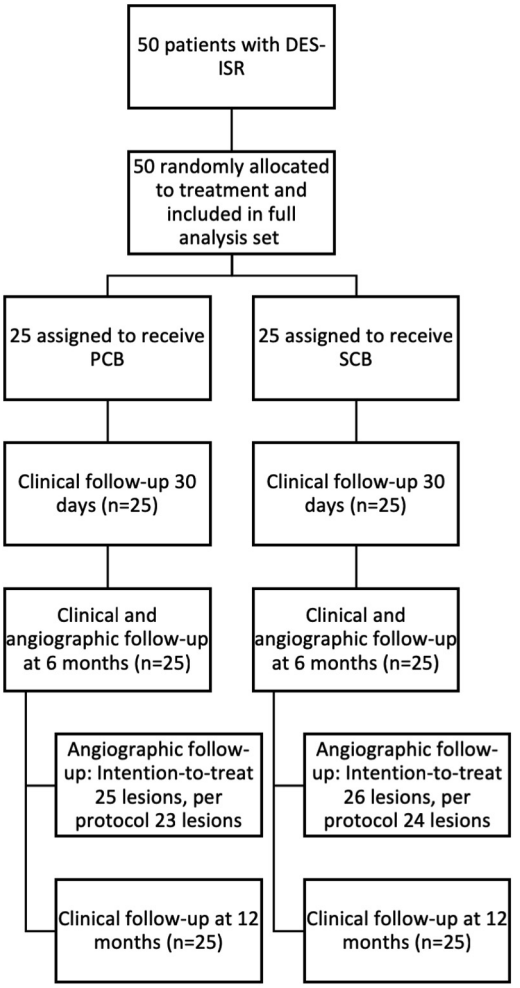
TABLE 2 Procedural Data

	PCB	SCB	p Value
Patients	25	25	
Lesions	25	26	
Severity of CAD			
1	3/25 (12)	6/25 (24)	0.426
2	11/25 (44)	7/25 (28)	
3	11/25 (44)	12/25 (48)	
Left ventricular ejection fraction, %	56.1 ± 13.5 (15)	56.9 ± 7.4 (15)	0.838
TIMI flow grade before procedure			
2	1	2	NS
3	24	24	
Diameter of previous implanted stents (mm)	2.9 ± 0.4 (21)	2.7 ± 0.3 (22)	0.431
Length of previous implanted stents (mm)	26.6 ± 11.0 (21)	26.0 ± 7.9 (21)	0.847
% stenosis (visual estimation by operator)	83.2 ± 10.7 (25)	77.4 ± 10.9 (26)	0.061
Study balloons	1.0 ± 0.2 (25)	1.1 ± 0.3 (26)	0.584
Balloon pressure (atm)	10.3 ± 2.8 (25)	11.6 ± 3.2 (26)	0.123
Balloon inflation time (s)	59.3 ± 6.1 (25)	59.0 ± 7.1 (26)	0.847
TIMI flow grade 3 at end of procedure	25 (100)	26 (100)	
Final diameter stenosis (%)	5.8 ± 6.0 (25)	7.1 ± 9.1 (26)	0.559
Dissection	0/25 (0)	1/25 (4)	NS

Values are n/N (%) or mean ± SD (n), unless otherwise indicated.

CAD = coronary artery disease; NS = not significant; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

FIGURE 1 Flow Chart of the Study



DES = drug-eluting stent(s); ISR = in-stent restenosis; PCB = paclitaxel-coated balloon; SCB = sirolimus-coated balloon.

QUANTITATIVE CORONARY ANGIOGRAPHY. Angiography was performed before and after all interventions and at angiographic follow-up using identical projections and analyses. Blinded investigators performed quantitative analysis of the coronary angiographic images (independent core lab, Homburg, Germany). The CAAS II Research System (Pie Medical Imaging, Maastricht, the Netherlands) was used for automated contour detection and quantification. Measurements were obtained in the stented area with measurement shoulder to shoulder (in-stent), and in the total stented area plus 5 mm proximally and distally (in-segment). Restenosis was defined as >50%

TABLE 3 QCA Intention-to-Treat Analysis

	PCB (n = 25)	SCB (n = 26)	p Value
Lesion length pre-PCI, mm	13.29 ± 7.18	14.24 ± 7.83	0.654
RFD pre-PCI, mm	2.42 ± 0.54	2.53 ± 0.53	0.483
MLD pre-PCI in lesion, mm	0.80 ± 0.52	0.81 ± 0.34	0.875
MLD pre-PCI in segment, mm	0.80 ± 0.52	0.81 ± 0.35	0.910
Diameter stenosis pre-PCI, %	69.3 ± 19.6	67.4 ± 13.5	0.688
MLD post pre-dilatation in lesion, mm	2.00 ± 0.57	2.09 ± 0.41	0.535
MLD post pre-dilatation in segment, mm	1.79 ± 0.75	1.94 ± 0.58	0.448
Diameter stenosis post pre-dilatation, %	22.8 ± 19.7	15.3 ± 11.5	0.151
Study device diameter, mm	2.93 ± 0.37	2.91 ± 0.39	0.821
RFD final, mm	2.40 ± 0.52	2.46 ± 0.49	0.692
MLD final in-lesion, mm	2.43 ± 0.41	2.28 ± 0.30	0.136
MLD final in-segment, mm	2.30 ± 0.42	2.08 ± 0.54	0.117
Diameter stenosis final, %	5.4 ± 4.3	8.3 ± 4.2	0.028
Acute gain, mm	1.63 ± 0.67	1.44 ± 0.44	0.235
FU, days	172.7 ± 83.1	186.1 ± 11.8	0.420
RFD FU, mm	2.38 ± 0.49	2.44 ± 0.45	0.705
MLD FU in-lesion, mm	2.06 ± 0.63	2.03 ± 0.49	0.885
MLD FU in-segment, mm	1.99 ± 0.59	1.99 ± 0.48	0.982
Diameter stenosis follow-up, %	19.9 ± 19.6	17.8 ± 20.4	0.713
LLL in-lesion, mm	0.37 ± 0.59	0.26 ± 0.57	0.479
LLL in-segment, mm	0.31 ± 0.62	0.18 ± 0.54	0.433

Values are mean ± SD.

FU = follow-up; LLL = late lumen loss; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RFD = reference diameter; other abbreviations as in Table 1.

diameter stenosis at angiographic follow-up. Patterns of ISR were defined according to the Mehran classification (30).

FOLLOW-UP AND ENDPOINTS. Dual antiplatelet therapy was continued orally for 1 month in stable patients or 12 months in case of acute coronary syndrome patients, followed by treatment with aspirin or clopidogrel alone. Patients underwent follow-up angiography after 6 months (up to 9 months). Clinical follow up was performed at 30 ± 7 days, at 6 months ± 4 weeks, and at 12 months ± 4 weeks post-procedure. All clinical endpoints and adverse events were evaluated in consensus by the investigators. All events were cross-checked with the medical records by external monitors and evaluated by an external physician (B.S.) who was blinded for the treatment groups. Due to the different package of the study balloon catheters, the investigators performing the study procedures were not blinded to the treatment assignment. However, angiographic core laboratory personnel and statistician were blinded to the treatment assignment.

TABLE 4 QCA Per-Protocol Analysis

	PCB (n = 23)	SCB (n = 24)	p Value
Lesion length pre-PCI, mm	13.16 ± 7.47	14.48 ± 8.11	0.564
RFD pre-PCI, mm	2.37 ± 0.53	2.50 ± 0.53	0.403
MLD pre-PCI in lesion, mm	0.83 ± 0.52	0.81 ± 0.32	0.883
MLD pre-PCI in segment, mm	0.83 ± 0.52	0.81 ± 0.33	0.847
Diameter stenosis pre-PCI, %	67.8 ± 19.7	67.2 ± 13.1	0.906
MLD post pre-dilatation in lesion, mm	2.06 ± 0.55	2.09 ± 0.42	0.858
MLD post pre-dilatation in segment, mm	1.83 ± 0.77	1.93 ± 0.60	0.626
Diameter stenosis post pre-dilatation, %	19.8 ± 17.7	15.0 ± 11.8	0.338
Study device diameter, mm	2.92 ± 0.39	2.90 ± 0.41	0.859
RFD final, mm	2.35 ± 0.52	2.43 ± 0.48	0.602
MLD final in lesion, mm	2.41 ± 0.41	2.28 ± 0.31	0.222
MLD final in segment, mm	2.27 ± 0.42	2.16 ± 0.35	0.346
Diameter stenosis final, %	5.8 ± 4.3	8.2 ± 4.2	0.080
Acute gain, mm	1.58 ± 0.67	1.46 ± 0.43	0.497
FU, days	174.7 ± 86.2	185.6 ± 11.9	0.540
RFD FU, mm	2.33 ± 0.48	2.41 ± 0.46	0.582
MLD FU in lesion, mm	2.13 ± 0.60	2.03 ± 0.50	0.530
MLD FU in segment, mm	2.06 ± 0.56	1.99 ± 0.50	0.678
Diameter stenosis FU, %	16.1 ± 15.5	17.8 ± 20.9	0.761
LLL in lesion, mm	0.28 ± 0.51	0.25 ± 0.58	0.857
LLL in segment, mm	0.21 ± 0.54	0.17 ± 0.55	0.794

Values are mean ± SD.

Abbreviations as in Tables 1 and 3.

Angiographic late lumen loss (LLL) (difference between the post-procedural and 6-month follow-up in-segment minimal lumen diameter; evaluated by quantitative coronary angiography) was the primary endpoint (intention to treat). Secondary endpoints included procedural success (<30% final stenosis, Thrombolysis In Myocardial Infarction flow grade 3, no flow-limiting dissection, and the absence of in-hospital major adverse cardiovascular events [MACE]), MACE (occurrence of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization) at 6 months and 12 months, as well as

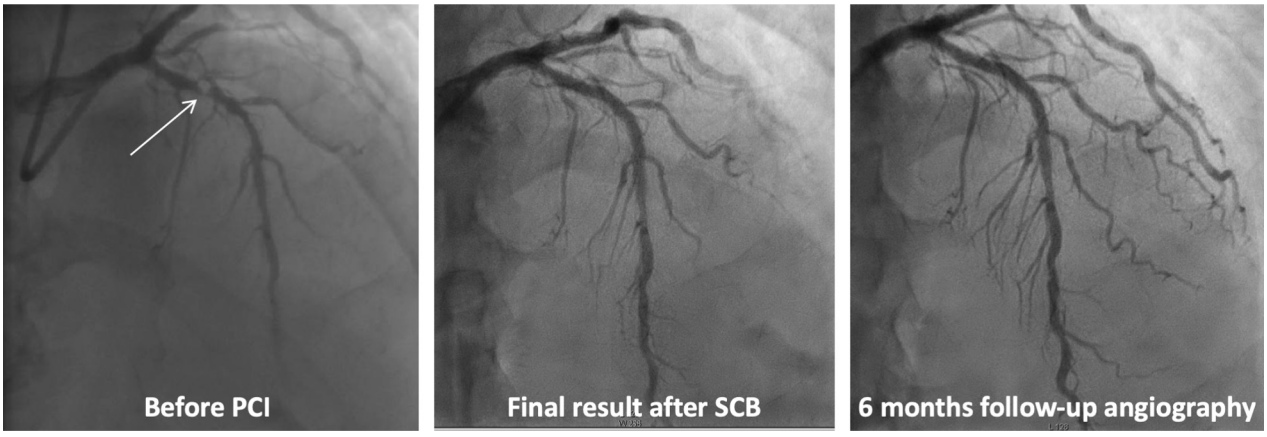
TABLE 5 Clinical Follow-Up at 1 Year, Intention-to-Treat Analysis

	PCB (n = 25)	SCB (n =25)	p Value
TLR	4 (16)	3 (12)	>0.99
Stent thrombosis	1	0	
Death	0	0	
Unscheduled angiography	0	2	
MACE	4 (16)	3 (12)	>0.99

Values are n (%), unless otherwise indicated. Major adverse cardiovascular events included cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization (TLR).

Abbreviations as in Table 1.

FIGURE 2 First Patient Treated With the SCB for DES Restenosis



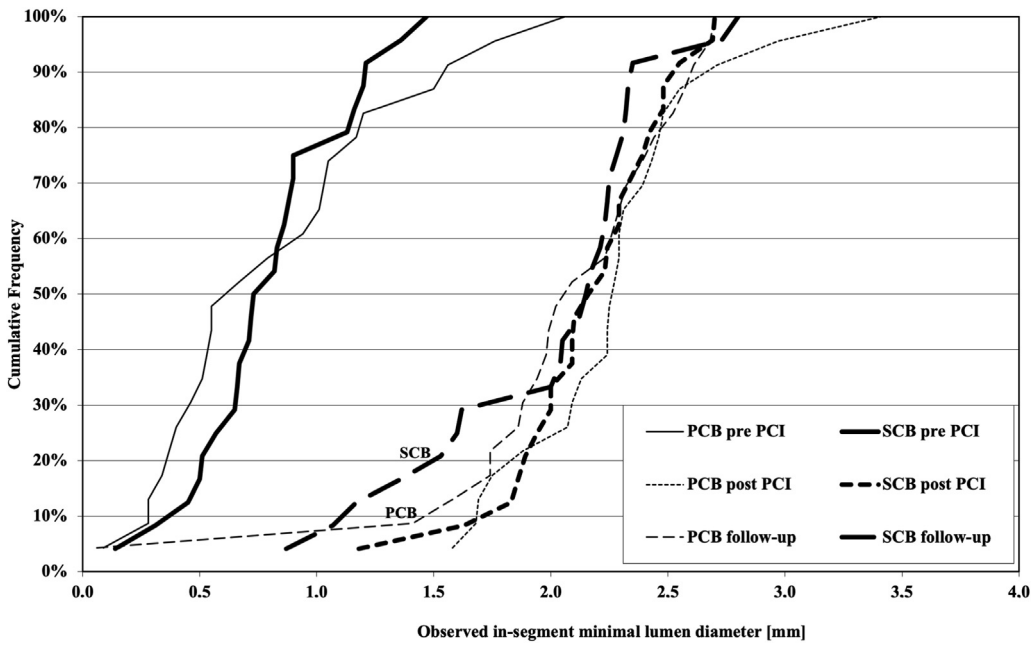
(Left) high-grade ISR in the proximal left anterior descending artery. **(Middle)** final result after angioplasty and SCB. **(Right)** angiographic control after 6 months without any signs of repeated restenosis. PCI = percutaneous coronary intervention; other abbreviations as in Figure 1.

individual clinical endpoints at 6 and 12 months follow-up (stent thrombosis, cardiac death, target lesion myocardial infarction, clinically driven target lesion revascularization, and angiographic binary restenosis).

Stent thrombosis, cardiac death, target lesion myocardial infarction, and clinically driven target lesion revascularization were defined according to the Academic Research Consortium (ARC) consensus document (31).

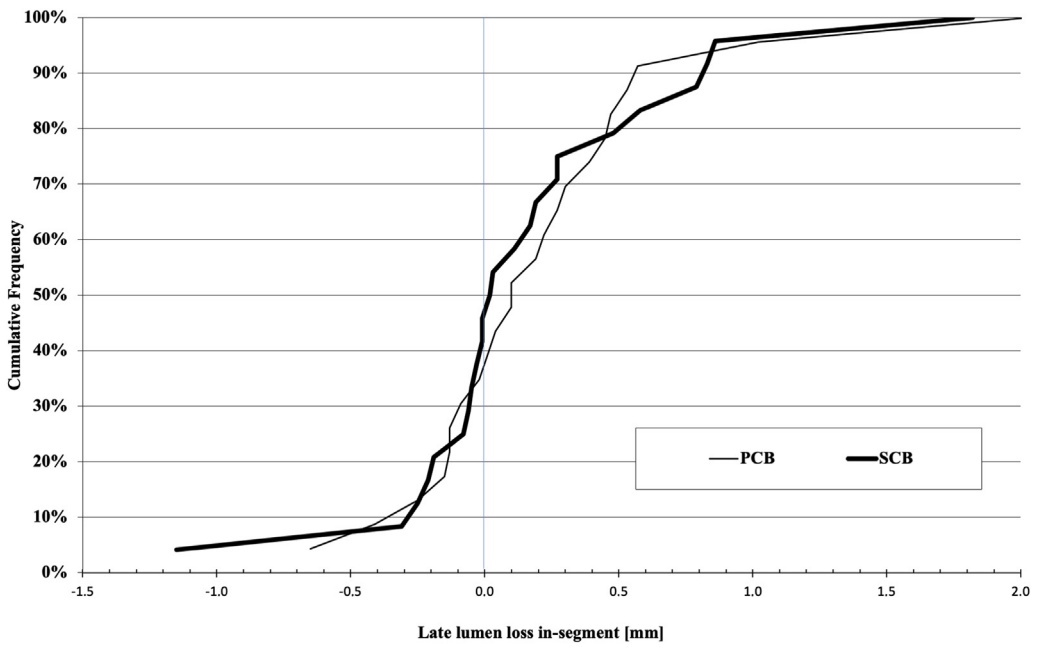
STATISTICAL ANALYSIS. The purpose of this study was to prove the noninferiority in terms of LLL of the SCB as compared with the PCB. The mean LLL in the

FIGURE 3 Angiographic Patency: Cumulative Frequency Distribution of In-Segment Minimal Lumen Diameter Determined by Quantitative Coronary Angiography



Per-protocol analysis. PCB versus SCB: before procedure (pre-PCI), post-procedure (post-PCI), and at 6 months (follow-up). Abbreviations as in Figures 1 and 2.

FIGURE 4 **Angiographic Patency: Cumulative Frequency Distribution of In-Segment Late Lumen Loss Determined by Quantitative Coronary Angiography**



Per-protocol analysis, PCB versus SCB. Abbreviations as in Figures 1 and 2.

SCB group was denoted with πS and in the PCB group with πP. The clinically relevant difference between those means was defined by $\delta = 0.35$ mm using a common SD of 0.40 mm, a power of 80%, and a 1-sided alpha of 2.5% according to European Medicines Agency guidelines for noninferiority testing. The corresponding test hypothesis was as follows: null hypothesis: $\pi S \geq \pi P + \delta$, alternative hypothesis: $\pi S < \pi P + \delta$. A total of 22 subjects were calculated to be sufficient to reject the null hypothesis. Accounting for 15% lost to follow-up 25 patients should be recruited per group ($N = 50$).

The primary endpoint LLL was analyzed in all patients with angiographic follow-up. Statistical analyses were conducted for the intention-to-treat population consisting of all data of patients who were recruited and randomized in this study, and the per-protocol population. Non-Gaussian samples are described by median and range. Discriminant variables are evaluated with the 2-sided Fisher's exact test.

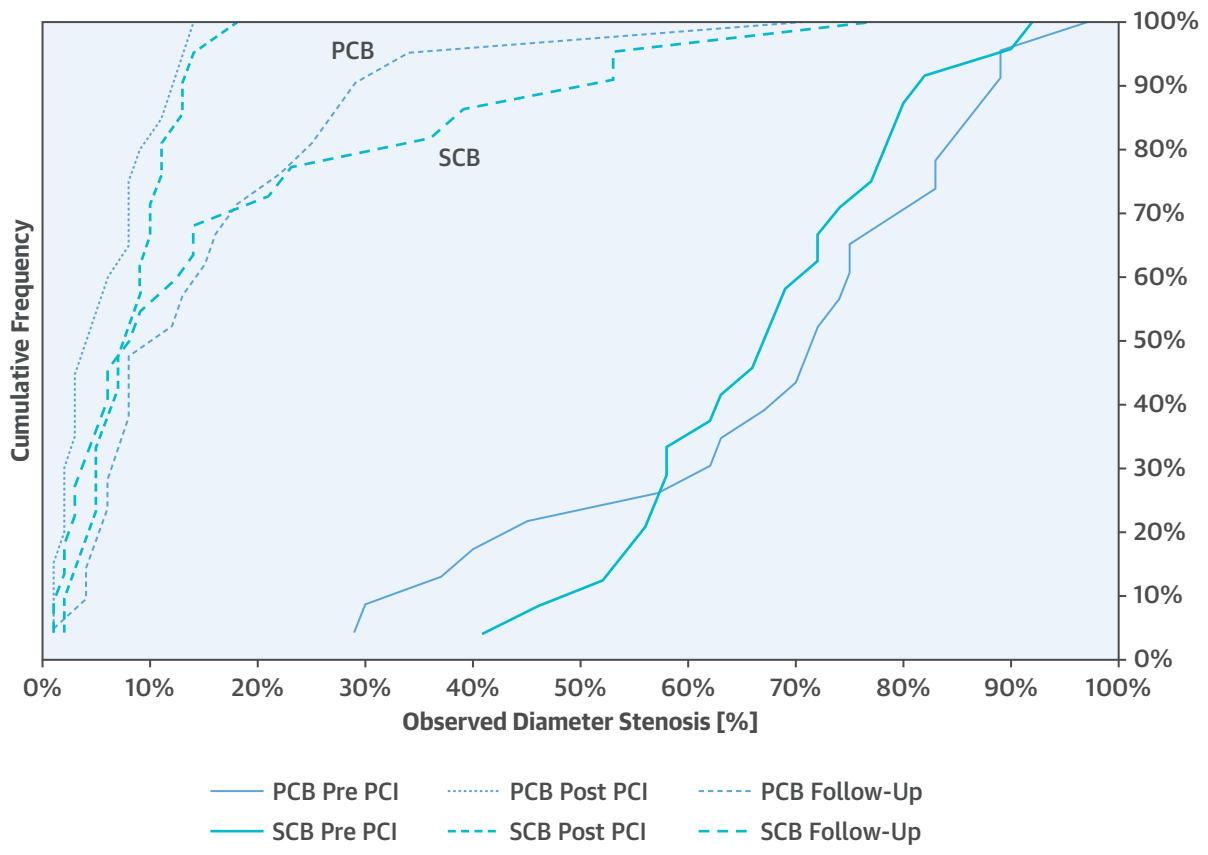
RESULTS

Fifty patients with DES ISR were enrolled in this randomized study between December 2015 and January 2017. Twenty-five patients were randomly assigned to the SCB group and 25 to the PCB group. Baseline characteristics of the patients were similar in the 2 groups (Table 1); 82% of patients were men and 44% presented with acute coronary syndrome. Most of the patients were diabetics (74%) and had multivessel coronary artery disease. Table 2 summarizes the procedural data.

Two patients in the PCB group were excluded from the per-protocol analysis, 1 patient due to geographical mismatch, and another patient due to treatment of an ISR in a saphenous venous bypass graft. In the SCB group, in 1 patient the angiographic baseline data were incomplete. Furthermore, in 1 bifurcation treatment of the SCB group, only the main branch was selected for the per-protocol analysis. The study flow chart is presented in Figure 1.

Quantitative coronary angiography revealed no differences in baseline parameters (Table 3). After 6 months, in-segment LLL was 0.31 ± 0.62 mm in the PCB group versus 0.18 ± 0.54 mm in the SCB group ($p = NS$; intention to treat) (Table 3). Per protocol, LLL was 0.21 ± 0.54 mm in the PCB group versus 0.17 ± 0.55 mm in the SCB group ($p = NS$) (Table 4). Clinical events during 12 months of follow-up also did not differ between the groups (Table 5). In the PCB group, 4 MACE occurred at a median of 182 days (range 178 to

CENTRAL ILLUSTRATION **Angiographic Patency: Cumulative Frequency Distribution of Diameter Stenosis Determined by Quantitative Coronary Angiography**



Ali, R.M. et al. J Am Coll Cardiol Intv. 2019;12(6):558–66.

Per-protocol analysis, PCB versus SCB: before procedure (pre-PCI), post procedure (post-PCI), and at 6 months (follow-up). Abbreviations as in Figures 1 and 2.

194 days), in the SCB group 3 MACE occurred at 182 days (range 182 to 187 days). Figure 2 shows the angiographic baseline and follow-up of the first patient treated with the SCB. Figures 3 and 4 and the Central Illustration present the cumulative frequency distribution of in-segment minimal lumen diameter, diameter stenosis, and LLL, respectively.

DISCUSSION

As an alternative to the implantation of another stent, the treatment of ISR with a PCB has proven to be clinically effective (4). After 1 year, similar recurrence rates were observed with DES and PCB (5-7,14-17,32-36) leading to the Class I, Level of Evidence: A recommendation for the treatment of coronary ISR in the 2014 and 2018 European guidelines (3). In addition, there is evidence that long-term hard clinical endpoints are positively influenced by the absence of a further layer of metal (9,10). However, the result after PCB therapy of ISR depends decisively on the quality of lesion preparation (12,37). The absence of flow-limiting dissections and a residual stenosis not more than 30% could be identified as quality criteria (38,39). But even with optimal predilation, the renewed revascularization after treatment of DES restenosis is higher than after BMS restenosis (5). In addition to improvements in the field of lesion preparation, balloon coatings with sirolimus analogs could theoretically also be advantageous, especially in the therapy of DES restenosis.

Several different concepts for the local balloon-based administration of sirolimus or its analogs have been proposed (25-29). First clinical experience was reported from 50 patients with ISR treated with sirolimus in a liquid formulation delivered by a

porous balloon (SABRE [Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis] trial). In this patient population, in-segment LLL at 6 months was 0.31 ± 0.52 mm (40). Another concept for balloon coating is the encapsulation of sirolimus in phospholipids (28). So far, only registry data have been presented, so that ultimately no statement on the effectiveness can be made. Data from a nonrandomized study on the treatment of de novo lesions of the superficial femoral artery using biodegradable polymers intermixed with sirolimus on a balloon reported a median of LLL of 0.19 mm in 34 patients undergoing reangiography (Thomas Zeller, oral presentation, Leipzig Interventional Course, January 2018). The LLL of 0.21 ± 0.54 mm (per protocol) observed with the PCB in this trial compares well with the LLL of PCB arms of other randomized trials in DES ISR, for example, 0.32 ± 0.55 mm in the PEPCAD (Paclitaxel-Eluting PTCABalloon Catheter in Coronary Artery Disease)-DES study (5), 0.46 ± 0.51 mm in the PEPCAD China study (8), and 0.30 ± 0.6 mm in the RIBS (Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent) IV study (14).

The crystalline coating investigated in the present study showed excellent drug transfer rates and a persistence of sirolimus in the tissue of about 50% of the initial concentration 4 weeks after application in the porcine coronary model (29). In contrast, the encapsulation of sirolimus in phospholipids resulted in a decline of the initial tissue concentration to about 4% already after 2 weeks (28). It remains to be seen whether these differences in the preclinical models will be reflected in differences in clinical efficacy.

This randomized study systematically investigates for the first time the antirestenotic efficacy of a SCB compared with the clinically established and here considered gold standard PCB (SeQuent Please Neo). Interestingly, both DCBs showed almost identical angiographic courses with very low lumen loss in this risk group in the treatment of DES restenosis after 6 months. This is the first indication that SCBs are as effective as best-in-class PCBs, at least in this indication and in a relatively short follow-up time.

STUDY LIMITATIONS. These results need to be confirmed in further studies and the question of longer-term efficacy has to be investigated. A limitation of this pilot trial is the relatively low sample size of 50 subjects. This allows not for further conclusions on the safety and efficacy of the SCB. The observed trend for a numerically lower LLL needs to be confirmed in larger clinical trials. Furthermore, it is currently unclear whether the lumen enlargement seen in de novo stenoses after PCB treatment (41,42) due to a kind of Glagov effect (43) also occurs with sirolimus, as the transverse distribution of paclitaxel and sirolimus in the vessel wall is very different (44).

CONCLUSIONS

This first-in-man comparison of a novel SCB with a crystalline coating shows similar angiographic and clinical outcomes in the treatment of coronary DES ISR compared with the PCB with the largest clinical evidence.

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PERSPECTIVES

WHAT IS KNOWN? PCBs are standard of care for the therapy of coronary ISR. With comparable clinical results, they do not require the implantation of an additional metal layer and may lead to better long-term results.

WHAT IS NEW? So far, positive data from randomized clinical trials for the therapy of ISR were only available for PCBs, in particular almost exclusively for paclitaxel iopromide-coated balloon catheters. In the present study, a comparable angiographic efficacy of a new SCB with a crystalline coating could be demonstrated for the first time in a small number of cases.

WHAT IS NEXT? The results must be verified in larger numbers of cases. Furthermore, this new technology should also be investigated in de novo lesions.

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KEY WORDS coronary in-stent restenosis, paclitaxel-coated balloon, sirolimus-coated balloon