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NEW RESEARCH PAPER

A Prospective Randomized Trial Comparing Sirolimus-Coated Balloon With Paclitaxel-Coated Balloon in De Novo Small Vessels

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ABSTRACT

BACKGROUND There are no data comparing sirolimus-coated balloons (SCBs [MagicTouch, Concept Medical]) to paclitaxel-coated balloons (PCBs [SeQuent Please Neo, B. Braun]) for the treatment of de novo small vessel disease (SVD).

OBJECTIVES This study sought to compare quantitative coronary angiographic outcomes at 6 months after treatment of de novo SVD with a PCB or SCB.

METHODS This prospective, multicenter, noninferiority trial randomized 121 patients (129 SVD lesions) to treatment with an SCB or PCB, with balloon sizing determined using optical coherence tomography. The primary endpoint was noninferiority for the 6-month angiographic net lumen gain.

RESULTS Angiographic follow-up was completed in 109 (90.1%) patients in the per-protocol analysis. The mean ± SD angiographic net gains were 0.25 ± 0.40 mm with SCBs vs 0.48 ± 0.37 mm with PCBs, resulting in SCBs failing to meet the 0.30 mm criterion for noninferiority ($P_{\text{noninferiority}} = 0.173$), with an absolute difference of −0.23 mm (95% CI: −0.37 to −0.09) secondary to a smaller late loss (mean ± SD: 0.00 ± 0.32 vs 0.32 ± 0.47 mm; $P < 0.001$) and more frequent late lumen enlargement (53.7% vs 30.0%; OR: 2.60; 95% CI: 1.22 to 5.67; $P = 0.014$) with PCBs. Binary restenosis rates were 32.8% and 12.5% following treatment with SCBs and PCBs, respectively (OR: 3.41; 95% CI: 1.36-9.44; $P = 0.012$). The mean ± SD angiography-derived fractional flow ratio at follow-up was 0.86 ± 0.15 following treatment with SCBs and 0.91 ± 0.09 following PCBs ($P = 0.026$); a fractional flow ratio ≤0.80 occurred in 13 and 5 vessels after treatment with SCBs and PCBs, respectively.

CONCLUSIONS The SCB MagicTouch failed to demonstrate noninferiority for angiographic net lumen gain at 6 months compared to the PCB SeQuent Please Neo. (J Am Coll Cardiol Intv 2023;■:■-■) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ANCOVA = analysis of covariance

DCB = drug-coated balloon

DES = drug-eluting stent

ISR = in-stent restenosis

ITT = intention-to-treat

LLE = late lumen enlargement

LLL = late luminal loss

LMCI = lower margin of the 1-sided 95% CI

MI = myocardial infarction

MLD = minimal lumen diameter

OCT = optical coherency tomography

PCB = paclitaxel-coated balloon

PES = paclitaxel-eluting stent

PP = per population

QCA = quantitative coronary angiography

QFR = fractional flow ratio

RCT = randomized controlled trial

RVD = reference vessel diameter

SCB = sirolimus-coated balloon

SVD = small vessel disease

TLR = target lesion revascularization

Contemporary drug-eluting stents (DESs) have shown exceptional antiproliferative efficacy and excellent short- and medium-term clinical outcomes. However, encaging vessels within a permanent metallic frame amplifies the risk of in-stent restenosis (ISR), neoatherosclerosis,[1] and very late stent thrombosis.[2] In contrast, drug-coated balloons (DCBs) avoid permanent implants and vessel caging, allowing shorter durations of dual antiplatelet therapy[3] while facilitating at medium- to longer-term follow-up late lumen enlargement (LLE), vessel remodeling, and pharmacologically induced plaque regression.[4]

Clinical studies showing the efficacy of DCBs compared to DESs have led to their Class I recommendation for the treatment of ISR,[5] whereas growing clinical evidence supports their role in treating de novo coronary lesions, especially in small vessel disease (SVD)[6-8] wherein implantation of a metallic prosthesis constitutes an even higher risk of restenosis than in large-caliber vessels.

Clinical data from randomized controlled trials (RCTs) of DCBs are primarily based on studies of PCBs, putatively related to their favorable pharmacokinetic properties.[9] In contrast, all contemporary DESs elute sirolimus or limus analogues following their superior outcomes compared to paclitaxel-eluting stents (PESs) across all indications, including SVD,[10] and the observed increased risk of stent thrombosis with PESs compared to bare-metal stents and nonpaclitaxel DESs.[11] However, although sirolimus offers improved safety and efficacy and a greater antirestenotic and anti-inflammatory effect than paclitaxel when eluted from a coronary stent, its use on a DCB, which requires rapid drug release and short transfer times, may be hampered by its low lipophilicity and low penetration and retention in the target vessel wall. To date, data from RCTs on outcomes following treatment with sirolimus-coated balloons (SCBs) or comparisons of SCBs vs PCBs are limited.[12]

The MagicTouch SCB (Concept Medical) was developed using a novel technology with encapsulation of low lipophilicity sirolimus into a protective lipophilic package.[13] The objective of this pilot study was to investigate the efficacy and safety of this SCB compared to a conventional PCB (SeQuent Please Neo, B. Braun) for the treatment of de novo SVD.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The TReAtmeNt of Small Coronary Vessels: MagicTouch Sirolimus Coated Balloon (TRANSFORM I) study (NCT03913832) is a prospective, randomized, multicenter, open-label noninferiority trial conducted in Europe[14] that enrolled 121 patients with stabilized acute coronary syndrome or chronic coronary syndrome who had at least ≥1 de novo coronary artery lesion in a small coronary vessel (defined as a reference vessel diameter [RVD] <2.75 mm by quantitative coronary angiography [QCA]). The full inclusion and exclusion criteria are shown in Supplemental Table 1. Patients were randomized 1:1 to treatment with the study (MagicTouch SCB) or control (SeQuent Please Neo PCB) device. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent for participation in the trial.

STUDY DEVICES. The MagicTouch is coated with sirolimus in a uniform manner using a spray coating, whereas its novel Nanolute technology overcomes sirolimus's low lipophilicity by encapsulating it in a protective lipophilic package, which allows drug diffusion, penetration, and midterm residency in the arterial wall following balloon inflation (Supplemental Figures 1 and 2). This package consists of microspheres with a diameter of 100 to 300 nm, giving a total dose of 1.27 μg/mm^2, which is well within the therapeutic window of sirolimus.[14] The sirolimus is distributed circumferentially over the balloon surface and within the balloon folds, with

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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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approximately 66% remaining inside these folds and only 34% exposed to blood before balloon deployment, thereby minimizing drug loss during transit (Supplemental Figure 3). The comparator device is the SeQuent Please Neo PCB, which is coated with 3 μg/mm^2 paclitaxel; it has been widely studied in preclinical and clinical studies, which have already detailed the paclitaxel release kinetics.[9]

PROCEDURES. Predilatation was recommended using a compliant or noncompliant balloon with a balloon-to-vessel ratio of 0.8 to 1.0 and an inflation pressure more than nominal. Predilatation was considered successful, as assessed by the investigators, by the absence of 1) major angiographic dissections (type C, D, E, or F) according to the National, Heart, Lung, and Blood Institute classification and 2) a Thrombolysis In Myocardial Infarction trial flow grade ≤2. Only lesions having undergone successful predilatation (n = 121) were randomized.[15]

Optical coherency tomography (OCT) was performed after predilatation. The OCT-derived lumen-based balloon sizing approach was used (Supplemental Figure 4)[14] with the DCB diameter selected according to the respective DCB compliances (Supplemental Table 2). These different approaches in selecting balloon sizes were aimed at minimizing balloon-induced coronary dissection, together with optimizing wall apposition and drug transfer to the vessel wall for each respective balloon. Retrospectively, to elucidate the influence of the extent of dissection on angiographic outcomes, dissection was quantitatively assessed by OCT (QCU-CMS, Leiden University Medical Center). Tissue composition was also retrospectively assessed by OCT deep learning (OctPlus, Pulse Medical Imaging Technology). The detailed methods on quantification of the dissection volume and tissue composition are described in Supplemental Figures 5 to 7.

DCB treatment was performed after OCT assessment. It was recommended that the DCBs were delivered to the target lesion ≤45 seconds with a single inflation performed for 60 seconds (irrespective of which DCB) at a pressure between nominal and rated burst according to each compliance chart. Detailed pre- and postprocedural antiplatelet regimens are shown in Supplemental Table 3.

QUANTITATIVE CORONARY ANGIOGRAPHIC ASSESSMENTS. Coronary angiograms were performed at baseline, post-predilatation, post-DCB, and at the 6-month follow-up and analyzed off-line using validated QCA software (CAAS, Pie Medical Imaging) by certified analysts at an independent core laboratory (CORRIB Corelab).

To precisely identify the position of the DCB in the treated vessel, cinefilming of the inflated DCB and the angiogram of the vessel performed after retrieval of the DCB were electronically superimposed. QCA analyses of the "DCB treated area" and "in-segment area" were performed on the angiographic images of the inflated DCB and the vessel angiogram post-DCB treatment (Supplemental Figure 8). In-segment analysis was defined as the DCB treated area plus a proximal and distal 5-mm segment. This methodology was meticulously applied to accurately circumscribe the same region of interest post-treatment and at follow-up and to detect possible geographic miss, defined as incomplete coverage of the area/length of the dilating balloon by the area/length of the DCB. Geographic miss was classified as 1) none, 2) partial, or 3) complete (Supplemental Figure 9).

Given this stringent methodological approach, the technique of a single "procedural" angiographic view filmed at baseline, post-DCB, and the 6-month follow-up was adopted for the assessment of the endpoint of acute gain (minimal lumen diameter [MLD] at post-DCB − MLD at baseline), late luminal loss (LLL [MLD at 6-month follow-up − MLD at post-DCB]), and net luminal gain (MLD at 6-month follow-up − MLD at baseline). In addition to the 1 single-matched paired angiographic view approach, MLD was also assessed using the average of multiple paired matched angiographic views of the treated coronary segment delineated by fiducial coronary branches to identify the "relocation" of the MLD outside the DCB treated area.

Angiography-derived fractional flow ratio (QFR) was documented at 6 months using Medis software to assist the clinical events committee in adjudicating "clinically and/or physiologically indicated target lesion revascularization (TLR)" according to the recommendations of the Academic Research Consortium-2.

STUDY ENDPOINTS. The primary endpoint was angiographic net gain in MLD (mm) inside the DCB treated area in the per-protocol (PP) population, which consisted of patients who received the assigned treatment in the absence of bail-out stenting. LLL is frequently used as an angiographic primary endpoint for DES; however, net gain is a more suitable surrogate endpoint in DCB studies because it represents the complex balance between late loss (proliferative process and constrictive remodeling) and late gain (potential plaque regression and expansive remodeling) in the absence of a metal cage. Detailed information on bail-out procedures is

described in the Supplemental Table 1. As described earlier, 1 single-matched paired angiographic view was used for the assessment of acute gain, LLL, net gain, and binary restenosis rate (percent diameter stenosis [%DS] ≥50%).

Additional prespecified secondary endpoints included device success (lesion based)[14]; procedure success; device-oriented composite endpoint defined as the composite of cardiac death, target vessel myocardial infarction (MI), and clinically and/or physiologically indicated TLR; and the incidence of acute/subacute/early/late vessel closure/thrombosis. Secondary endpoints are defined in Supplemental Table 4. Periprocedural MI was defined according to the Society for Cardiovascular Angiography and Interventions 2013 definition and spontaneous MI according to the fourth universal definition.[16] All patients had clinical follow-up at 6 months. All events were adjudicated by an independent clinical events committee blinded to study device. This 6-month report is based on data extract of October 6th, 2023. Final clinical data will be reported at 12 months follow-up.

STATISTICAL ANALYSIS. The trial was powered for noninferiority of the primary endpoint at the 6-month angiographic follow-up. A mean ± SD net gain of 0.87 ± 0.51 mm was expected in both device groups based on the net gain observed at 6 months in lesions treated with the SeQuent Please PCB in The Paclitaxel-Eluting PTCA-Balloon Catheter to Treat Small Vessel (PEPCAD) study.[17] Using a noninferiority margin of 0.30 mm and assuming an attrition rate of 10%, 57 patients per arm were required to achieve ≥85% power to demonstrate noninferiority with a 1-sided type "error of 0.05."[14]

Three sensitivity analyses were performed wherein the primary endpoint was assessed using an analysis of covariance (ANCOVA) linear regression model, intention-to-treat (ITT) population, OCT-defined SVD population (RVD <2.75 mm), and "in-segment" analysis. Despite the randomized nature of the study, the primary endpoint was adjusted for baseline RVD and MLD through an ANCOVA linear regression model in line with recommendations from the Food and Drug Administration and as prespecified in the statistical analysis plan. This analysis model provides an estimated difference in the mean net gain at 6 months between the 2 randomized groups conditional on these baseline variables. The lower margin of the 1-sided 95% CI (LMCI) of this mean difference was compared to the prespecified noninferiority limit of −0.30 mm. The analysis of clinical secondary endpoints was performed on the ITT population and was not powered. Kaplan-Meier estimates were censored at 300 days (9 months + 30 days) and used to analyze the occurrence of clinical events; Kaplan-Meier estimates are presented with 95% CIs. The linear regression models were used to estimate the association between LLL and acute gain/dissection volume. The 95% CIs for the coefficients of the linear model were plotted.

Continuous variables are presented as mean ± SD and were compared by the Student's *t*-test. Categoric variables were compared with the chi-square or Fisher exact test. A 2-sided P value < 0.05 was considered statistically significant. Analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing).

RESULTS

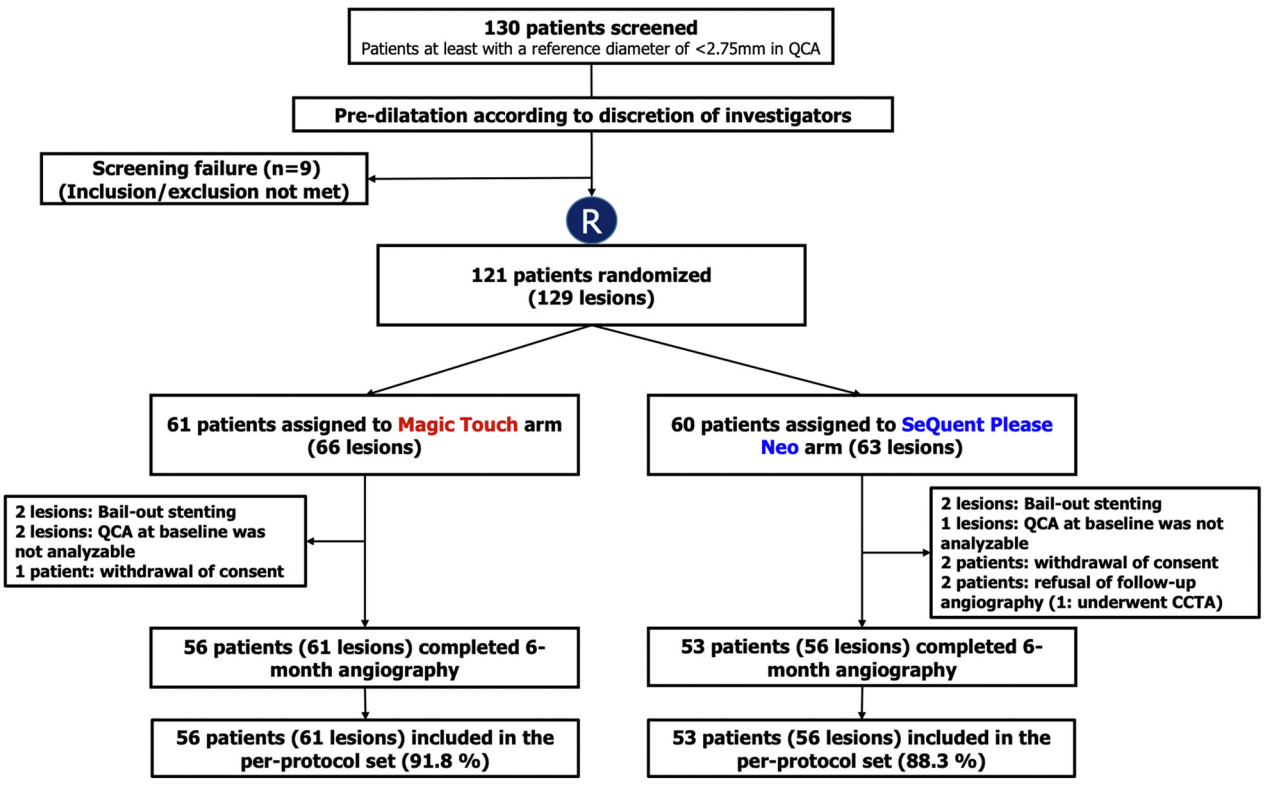
The study randomized 121 patients with 61 receiving SCBs (66 lesions) and 60 PCBs (63 lesions); however, as detailed in **Figure 1**, 11 patients were excluded, leaving 109 patients (90%) with 117 evaluable target lesions (SCB 61 lesions vs PCB 56 lesions) in the final PP set. The study population complied with the integrity and statistical power of the primary endpoint analysis.

Baseline patient and lesion characteristics are presented in **Table 1**. The mean age was 70 and 67 years in the SCB and PCB groups, respectively; the rates of diabetes, dyslipidemia, and hypertension were similar. Most of the treated lesions involved branches of the major epicardial arteries, in keeping with an SVD study.

Baseline procedural details are summarized in **Table 2**. There were no significant differences in device and procedural success rates (SCB 50.0% vs PCB 40.4%; OR: 0.68; 95% CI: 0.32-1.45; $P = 0.317$). The mean crossing time was numerically shorter with SCB (mean difference = −6.3 seconds [95% CI: -13 to -0.02]), whereas there were no significant differences in the mean inflation time. Histograms of RVD by QCA and OCT vs nominal size of DCB, which ensures proper apposition of the DCB and drug transfer to the vessel wall, are shown in Supplemental Figure 10. There were no significant between-group differences in the rates of acute recoil or geographic miss (**Table 2**).

ANGIOGRAPHIC OUTCOMES. Baseline angiographic analyses confirmed that lesion length, MLD, RVD, and %DS were well matched between groups (**Table 1**). The mean ± SD acute gain following SCB was 0.57 ± 0.37 mm compared to 0.50 ± 0.33 mm with PCB (difference = 0.07 [95% CI: −0.06 to 0.20]; **Table 3**). Angiographic follow-up was completed in 90.1% of patients (SCB 91.8%, PCB 88.3%) at a median time of 185 days (IQR: 173-202 days; **Figure 1**).

FIGURE 1 Study Flowchart



CCTA = coronary computed tomography angiography; QCA = quantitative coronary angiography.

The primary endpoint of the mean ± SD in-DCB net gain with SCB and PCB was 0.25 ± 0.40 mm vs 0.48 ± 0.37 mm (**Table 3**, **Figure 2A**), giving an absolute difference in net gain of −0.23 mm (95% CI: −0.37 to −0.09) and an LMCI of −0.35 mm, such that SCB failed to meet the −0.30 mm criterion for noninferiority ($P_{\text{noninferiority}} = 0.173$) vs PCB. This lower net gain was primarily caused by a smaller LLL (0.00 ± 0.32 vs 0.32 ± 0.47 mm, difference = −0.31 [95% CI: −0.17 to −0.46]; **Table 3**, **Figure 2B**) and more frequent LLE (53.7% vs 30.0%; OR: 2.60; 95% CI: 1.22-5.67; $P = 0.014$) with PCB compared to SCB.

The 4 prespecified sensitivity analyses are displayed in Supplemental Table 5. SCB failed to meet noninferiority in the ANCOVA analysis, ITT population, and OCT-defined SVD population where the LMCI was −0.30 mm, −0.31 mm, and −0.33 mm, respectively ($P_{\text{noninferiority}} = 0.057$, 0.075, and 0.114, respectively; Supplemental Table 5). The in-segment net gain was lower with SCB (mean ± SD: 0.24 ± 0.40 vs 0.45 ± 0.36 mm; absolute difference = −0.18; 95% CI: −0.31 to −0.06); however, in the corresponding ANCOVA analysis, the LMCI was −0.29 mm, achieving noninferiority ($P_{\text{noninferiority}} = 0.031$).

The other angiographic outcomes determined in the single procedural angiographic view are displayed in **Table 3**. Supplemental Figure 11 shows the cumulative frequency distributions of in-DCB MLD and %DS at baseline, post-DCB, and the 6-month follow-up. Angiographic %DS at follow-up was significantly higher in lesions treated with SCB, with correspondingly higher rates of binary restenosis (32.8% vs 12.5%; OR: 3.41; 95% CI: 1.36-9.44; $P = 0.012$). During follow-up angiography, patients treated with SCB had lower mean QFRs and more vessels with a QFR ≤0.80 (**Table 3**). The cumulative frequency distributions of MLD and %DS in coronary segment(s) delineated by 2 fiducial branching points using average measurements derived from multiple paired matched views are shown in Supplemental Figure 12. At the 6-month follow-up, 20.4% of lesions had an MLD outside the DCB treated area.

TABLE 1 Baseline Clinical and Lesion Characteristics

Patients	Overall, N = 121	SCB, N = 61	PCB, N = 60
Age	68 (62-74)	70 (63-74)	67 (59-72)
Male	105 (87)	55 (90)	50 (83)
Current smoker	23 (19)	16 (26)	7 (12)
Medically treated diabetes	30 (25)	15 (25)	15 (25)
Insulin	7 (5.8)	2 (3.3)	5 (8.3)
Hypertension	95 (79)	51 (84)	44 (73)
Dyslipidemia	99 (82)	50 (82)	49 (82)
Previous MI	37 (31)	17 (28)	20 (33)
PVD	2 (1.7)	1 (1.6)	1 (1.7)
COPD	6 (5.0)	4 (6.6)	2 (3.3)
History of heart failure	6 (5.0)	4 (6.6)	2 (3.3)
History of major bleeding	1 (0.8)	1 (1.6)	0 (0)
Renal failure	1 (0.8)	1 (1.6)	0 (0)
Previous PCI	62 (51)	31 (51)	31 (52)
Previous CABG	2 (1.7)	2 (3.3)	0 (0)
Number of target lesions			
1	113 (93.4)	56 (91.8)	57 (95)
2	8 (6.6)	5 (8.2)	3 (5.0)
Lesions	**Overall, N = 129**	**SCB, N = 66**	**PCB, N = 63**
TIMI flow (preprocedure)			
0	2 (1.6)	1 (1.5)	1 (1.6)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	4 (3.1)	1 (1.5)	3 (4.8)
3	123 (95.3)	64 (97)	59 (93.6)
Target vessel			
LAD	10 (7.9)	3 (4.7)	7 (11.3)
Diagonal	29 (23.0)	12 (18.8)	17 (27.4)
LCX	26 (20.6)	12 (18.8)	14 (22.6)
Obtuse marginal/ramus	29 (23.0)	18 (28.1)	11 (17.7)
RCA	7 (5.6)	5 (7.8)	2 (3.2)
PDA/PL	25 (19.8)	14 (21.9)	11 (17.7)
Bifurcation	51 (39.5)	26 (39.4)	25 (39.7)
AHA type B2/C lesion	36 (28.6)	21 (32.8)	15 (24.2)
RVD (OCT), mm	2.40 (2.10-2.62)	2.44 (2.15-2.63)	2.39 (2.08-2.54)
RVD (QCA), mm	2.05 (1.78-2.31)	2.12 (1.90-2.44)	1.99 (1.76-2.26)
Diameter stenosis, %	54 (46-61)	53 (45-62)	54 (46-61)
MLD, mm	0.94 (0.78-1.12)	0.98 (0.77-1.19)	0.90 (0.79-1.08)
Lesion length, mm	10.4 (7.2-14.9)	10.1 (6.6-14.8)	11.1 (8.1-15.1)

Values are n (%) or median (IQR).

AHA = American Heart Association; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; LAD = left anterior descending; LCX = left circumflex; MI = myocardial infarction; MLD = minimal lumen diameter; OCT = optical coherence tomography; PCB = paclitaxel-coated balloon; PCI = percutaneous coronary intervention; PDA = posterior descending artery; PL = posterolateral artery; PVD = peripheral vascular disease; QCA = quantitative coronary angiography; RCA = right coronary artery; RVD = reference vessel diameter; SCB = sirolimus-coated balloon; TIMI = Thrombolysis In Myocardial Infarction.

RELATIONSHIP BETWEEN ANGIOGRAPHIC ACUTE GAIN VS LATE LOSS. The relationship between angiographic acute gain and LLL is shown in **Figure 3A**. The slope of the 2 regression lines are 0.72 for SCB and 0.37 for PCB, with comparable intercepts (−0.09 and −0.18, respectively) and a interaction with assigned treatment ($P_{interaction} = 0.065$).

RELATIONSHIP BETWEEN DISSECTION VOLUME AS ASSESSED BY OCT AND ANGIOGRAPHIC LATE LOSS. Of 117 lesions included in the PP analysis, OCT dissection analysis was feasible in 106 lesions; OCT was not performed in 1 case, and in the remaining 10 cases dissection volume could not be quantified because of poor image quality. Dissection and intimal fractures post-balloon angioplasty and pre-DCB were seen by OCT in 97.2% of cases, whereas dissections on angiography were seen in 17%. At the proximal origin of the dissection, the dissection occurs at the thinnest intimal site with 372 μm and mainly fibrotic plaque (83% of lesions, Supplemental Figure 7).

The median dissection volume and length were 1.95 mm^3 (IQR: 0.58-3.90) and 6.0 mm (IQR: 2.9-10.2), respectively (Supplemental Figure 13). There was a significant and positive correlation between angiographic LLL and dissection volume (LLL = 0.049 × dissection volume + 0.181; $P = 0.035$) following SCB treatment, whereas the relationship was flat with a slightly negative slope (LLL = −0.010 × dissection volume + 0.071; $P = 0.035$; $P = 0.315$) following PCB. There was significant interaction ($P_{interaction} = 0.013$; **Figure 3B**).

CLINICAL OUTCOMES. Clinical outcomes were assessed in the ITT population and censored at 300 days (9 months + 30 days). No deaths or acute vessel closures occurred in either group; there were 4 periprocedural MIs (SCB: n = 3, PCB: n = 1). No unplanned TLRs occurred before the mandated 6-month angiographic follow-up, which identified a late vessel occlusion in 1 SCB patient (**Table 4**). Nine vessels (5 SCBs and 4 PCBs) with a QFR ≤0.80 at the 6-month follow-up underwent a physiologically indicated TLR (9.5% vs 8.0%, log-rank $P = 0.877$).

DISCUSSION

The principal finding of the TRANSFORM-I randomized trial is that in patients with de novo SVD, the MagicTouch SCB failed to demonstrate noninferiority compared to the SeQuent Please Neo PCB in terms of angiographic net gain at 6 months (**Central Illustration**).

POTENTIAL BENEFIT OF DCB OVER STENT IN DE NOVO SVD. The strongest recommendation for using DCBs is in the treatment of ISR[6]; however, there is growing clinical evidence of their efficacy in treating de novo lesions, especially in SVD.[6-8] In the latter

TABLE 2 Procedural Characteristics

	Overall, N = 129	SCB, N = 66	PCB, N = 63	Difference (95 CI)
Balloon predilation	128 (99)	65 (98)	63 (100)	1.5 (-6.0 to 2.9)
Type of predilation balloon				0.23 (-0.11 to 0.58)
Compliant	40 (31)	17 (26)	23 (37)	
Noncompliant	89 (69)	49 (74)	40 (63)	
Maximal diameter of predilation balloon, mm	2.34 ± 0.30	2.39 ± 0.30	2.29 ± 0.29	0.10 (-0.01 to 0.20)
Maximal length of predilation balloon, mm	18.2 ± 5.6	18.3 ± 5.6	18.1 ± 5.6	0.19 (-1.7 to 2.1)
Dissection after pre-dilation[a]				0.16 (-0.19 to 0.51)
Yes	14 (11)	7 (11)	7 (11)	
No	109 (84)	57 (86)	52 (83)	
Dissection type after predilation				0.21 (-0.15 to 0.56)
Type A	0 (0.0)	0 (0.0)	0 (0.0)	
Type B	10 (8.1)	5 (7.8)	5 (8.5)	
Type C	3 (2.4)	2 (3.1)	1 (1.7)	
Type D/E/F	1 (0.8)	0 (0)	1 (1.7)	
Dissection volume (OCT derived), mm^3	1.95 (0.58-3.90)	2.30 (0.63-3.91)	1.56 (0.56-3.45)	0.74 (-0.46 to 1.06)
Longitudinal dissection length (OCT derived), mm	6.0 (2.9-10.2)	6.3 (2.93-10.9)	5.8 (2.9-9.6)	0.5 (-1.20 to 2.50)
Successful delivery of DCB	128 (100)	65 (100)	63 (100)	0 (-0.35 to 0.35)
Crossing time, s	34 ± 18	31 ± 12	38 ± 22	-6.3 (-13 to -0.02)
DCB max diameter, mm	2.40 ± 0.28	2.47 ± 0.29	2.34 ± 0.26	0.13 (0.03-0.22)
DCB nominal length, mm	22.9 ± 6.0	23.0 ± 5.7	22.8 ± 6.2	0.25 (-1.8 to 2.3)
DCB max pressure, atm	9.47 ± 2.62	9.62 ± 2.61	9.30 ± 2.65	0.32 (-0.60 to 1.2)
DCB duration, s	72 ± 30	74 ± 20	70 ± 38	4.0 (-6.8 to 15)
Longitudinal geographic miss (Partial or Complete)[b]	31 (34.4)	18 (39.1)	13 (29.5)	-0.10 (-0.28 to 0.10)
Acute percent recoil	6.8 ± 1.4	5.0 ± 14.0	8.6 ± 14.2	-3.9 (-8.7 to 1.5)
Dissection after procedure[a]				0.22 (-0.12 to 0.57)
Yes	23 (18)	10 (15)	13 (21)	
No	105 (81)	55 (83)	50 (79)	
Dissection type after procedure				0.39 (0.04 to 0.74)
Type A	1 (0.8)	1 (1.5)	0 (0)	
Type B	16 (13)	7 (11)	9 (14)	
Type C	3 (2.4)	2 (3.1)	1 (1.6)	
Type D/E/F	3 (2.4)	0 (0)	3 (4.8)	
Bail out procedure performed	4 (3.1)	2 (3.0)	2 (3.2)	-0.14 (-6.3 to 6.0)

Values are n (%), median (IQR), or mean ± SD. [a]Dissection after predilation was not assessable in 6 cases and after the procedure in 1 case. [b]Definition of geographic miss was described in the Supplement. Difference is either difference in means, proportions, or standardized mean difference for >2 factor variables. 95% CI: 2-sided and no correction for clustering; all measures are at lesion level.

DCB = drug-coated balloon; other abbreviations as in Table 1.

group especially, this lack of vessel encasement, which facilitates LLE caused by positive vascular remodeling, is advantageous because it can offset the initial lower acute gains in luminal dimensions observed with DCBs compared to DESs. In the BELLO (Balloon Elution and Late Loss Optimization) DCB study, angioplasty with the IN.PACT Falcon PCB (Medtronic-Invatec) in SVD was associated with lower angiographic LLL and similar rates of restenosis and revascularization compared to PES at 6 months, whereas at 3 years major adverse cardiac event rates were significantly lower with the PCB (14% vs 30%; $P = 0.015$).[6] Similar trends in angiographic and 6-month clinical results were observed in the PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) study, which randomized patients with SVD to the Elutax SV PCB (Aachen Resonance) or an everolimus-eluting stent.[7]

Although these 2 clinical studies were conducted with PCBs, there is growing interest in SCBs, and although 2 sirolimus-coated devices are commercially available in Europe, objective comparative evidence from powered RCTs, especially against PCBs, is currently lacking.[12]

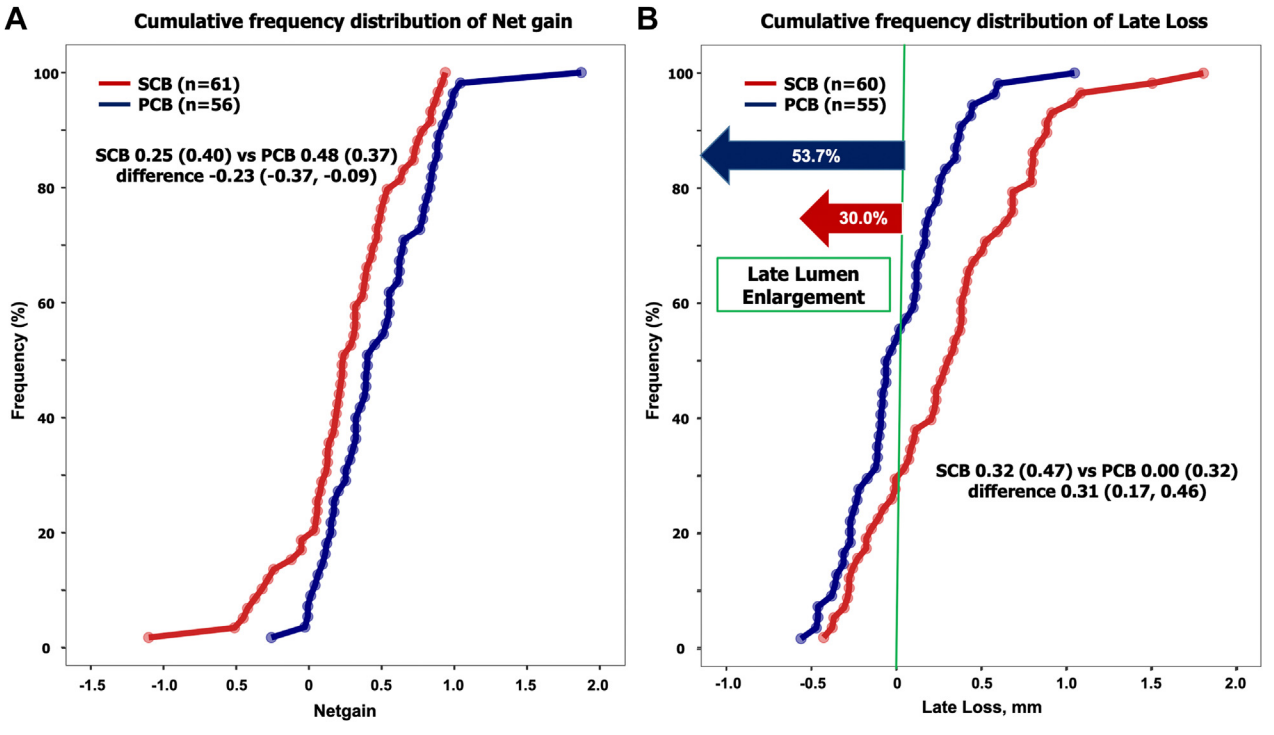
SIROLIMUS VS PACLITAXEL. Prior comparisons of paclitaxel and sirolimus are largely confined to early RCTs of the first-generation Taxus (Boston Scientific) PES vs the Cypher (Cordis) sirolimus-eluting stent[10] with both eluting drugs that inhibit the cell cycle,

TABLE 3 Angiographic Outcomes

	Overall	SCB	PCB	Difference (95% CI)
No. with angiographic follow-up	117	61	56	
Minimal lumen diameter, mm	1.29 ± 0.35	1.22 ± 0.37	1.36 ± 0.32	−0.14 (−0.27 to −0.01)
Diameter stenosis, %	39 ± 16	44 ± 17	34 ± 14	9.4 (3.8-15)
Binary restenosis	27 (23.1)	20 (32.8)	7 (12.5)	20.3 (5.6-34.9)
Acute gain, mm				
In-DCB	0.54 ± 0.35	0.57 ± 0.37	0.50 ± 0.33	0.07 (−0.06 to 0.20)
In-segment	0.50 ± 0.36	0.53 ± 0.38	0.47 ± 0.35	0.06 (−0.08 to 0.19)
Late lumen loss, mm				
In-DCB	0.17 ± 0.44	0.32 ± 0.47	0.00 ± 0.32	0.31 (0.17-0.46)
In-segment	0.16 ± 0.43	0.29 ± 0.48	0.01 ± 0.31	0.29 (0.14-0.44)
Net gain, mm				
In-DCB	0.36 ± 0.40	0.25 ± 0.40	0.48 ± 0.37	−0.23 (−0.37 to −0.09)
In-segment	0.34 ± 0.40	0.24 ± 0.40	0.45 ± 0.36	−0.22 (−0.36 to −0.08)
QFR	0.89 ± 0.13	0.86 ± 0.15	0.91 ± 0.09	−0.05 (−0.10 to −0.01)
QFR below 0.80	18 (15.4)	13 (21.3)	5 (8.9)	12.4 (0.0-25.0)

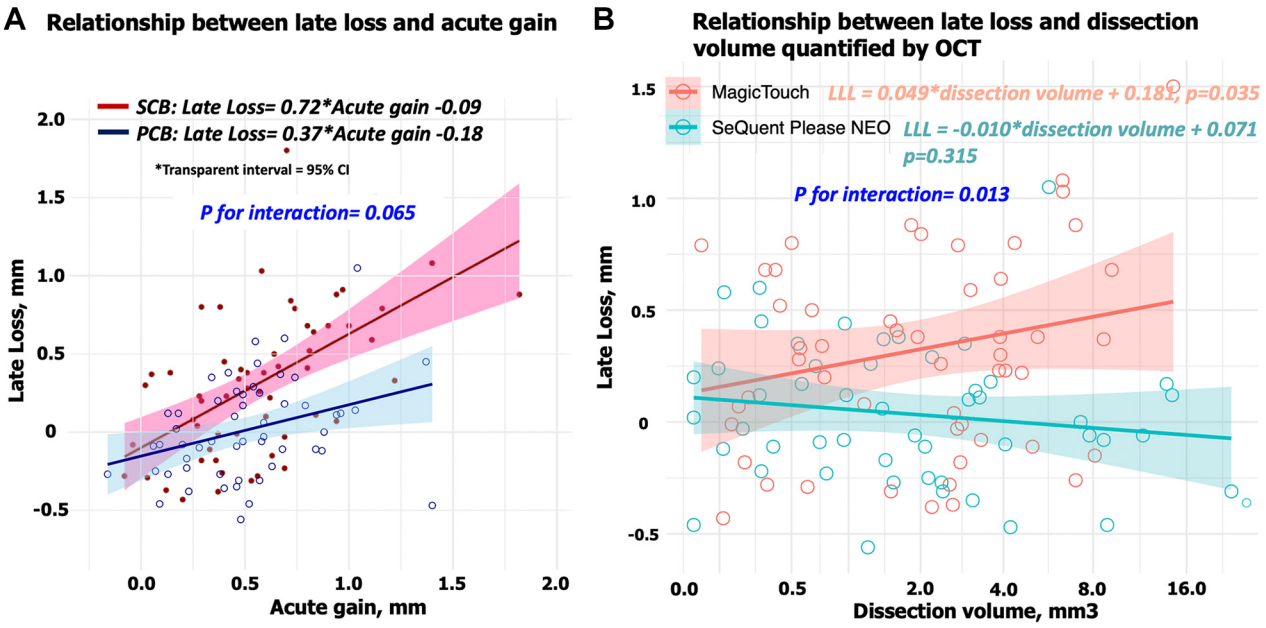
Values are n (%) or mean ± SD. Difference is either difference in means or proportions. 95% CI: 2-sided and no correction for clustering.

FIGURE 2 Cumulative Frequency Distributions of Late Loss and Net Gain



A and B show cumulative frequency distribution curve of net gain and late loss, respectively. PCB = paclitaxel-coated balloon; SCB = sirolimus-coated balloon.

FIGURE 3 Relationship Between Late Lumen Loss and Angiographic Acute Gain or Dissection Volume Quantified by OCT



(A) Relationship between angiographic late luminal loss (LLL) and acute gain. (B) Relationship between angiographic LLL and dissection volume quantified by optical coherence tomography (OCT). Abbreviations as in Figure 2.

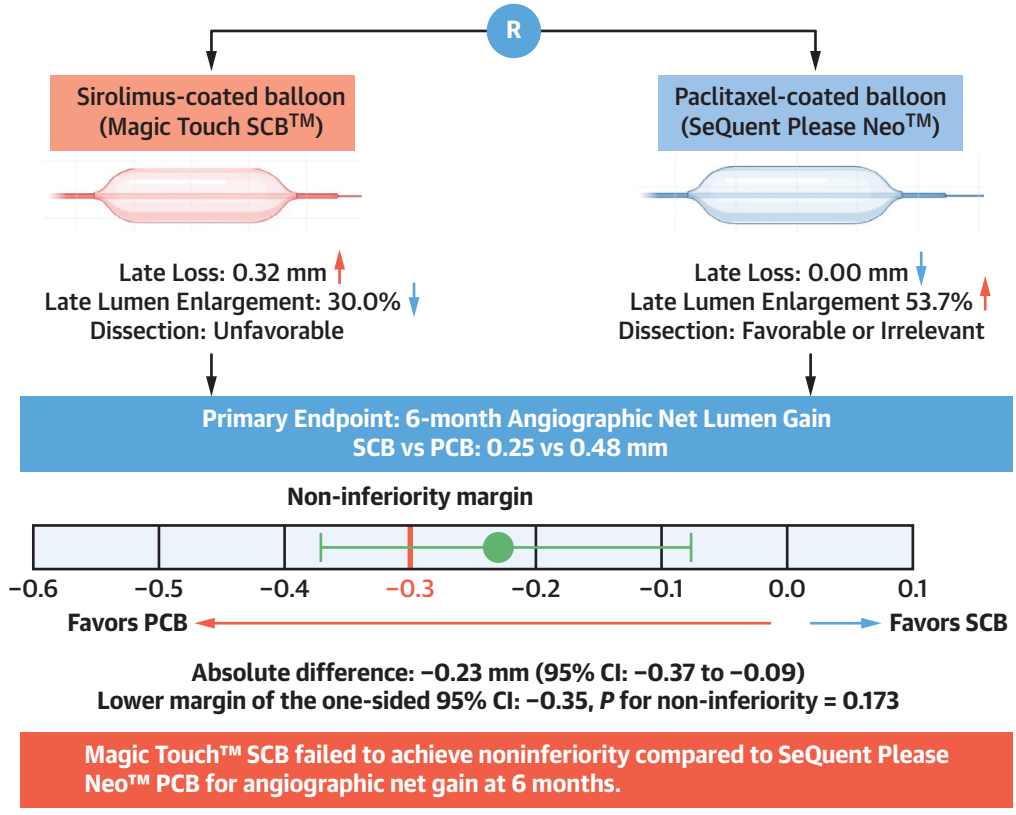
TABLE 4 Clinical Outcomes

	Overall	SCB		PCB		
Number of patients	121	61		60		
Discharge	**Events (n)**	**Events (n)**	**Incidence (%)**	**Events (n)**	**Incidence (%)**	***P* Value**[a]
Periprocedural MI	4	3	4.9	1	1.7	0.348
Acute closure/thrombosis	0	0	0.0	0	0.0	–
At follow-up[b]	**Events (n)**	**Events (n)**	**KM estimates (%), 95% CI**	**Events (n)**	**KM estimates (%), 95% CI**	***P* Value**[c]
DoCE	10	6	11.5 (5.4-23.9)	4	8.0 (3.0-19.9)	0.647
Death	0	0	–	0	–	–
MI	5	4	7.0 (2.7-17.7)	1	1.7 (0.2-11.3)	0.183
TV MI (spontaneous MI)	1	1	2.0 (0.3-13.6)	0	–	0.338
TLR	10	6	11.4 (5.3-23.6)	4	8.0 (3.0-19.9)	0.644
Clinically or physiologically indicated TLR	9	5	9.5 (4.1-21.3)	4	8.0 (3.0-19.9)	0.877
Non-TL TVR	6	4	7.8 (3.0-19.6)	2	4.2 (1.0-15.7)	0.438
Non-TVR	12	6	11.3 (5.2-23.5)	6	11.4 (5.3-23.8)	0.816
Late closure/thrombosis	1	1	1.9 (0.3-12.9)	0	–	0.342

[a]*P* value for logistic regression. [b]Censored at 300 days. [c]*P* value for log-rank.

DoCE = device oriented composite endpoint; KM = Kaplan-Meier; MI = myocardial infarction; TL = target lesion; TLR = target lesion revascularization; TV = target vessel; TVR = target vessel revascularization.

CENTRAL ILLUSTRATION **TRANSORM-I Trial: A Prospective, Multicenter, Noninferiority Trial in Patients With De Novo Small Vessel Coronary Artery Disease**



Ninomiya K, et al. J Am Coll Cardiol Intv. 2023;■(■):■-■.

PCB = paclitaxel-coated balloon; SCB = sirolimus-coated balloon.

albeit at different stages; sirolimus induces G1 cell cycle inhibition, whereas paclitaxel leads predominantly to M-phase arrest. Differences in efficacy between these DESs in terms of neointimal inhibition have been confirmed in multiple studies,[10,18] and although the eluted drug was likely key, the contribution from other factors such as stent platform, strut thickness, polymer type, and drug elution time cannot be ignored.

The commonest antiproliferative drug for DCBs is presently paclitaxel; however, sirolimus offers potential benefits in terms of safety and efficacy considering its wider safety therapeutic range and greater antirestenotic and anti-inflammatory effect, which are the major reasons PESs are no longer commercially available for use in coronary arteries.[19] In addition, despite the mechanisms being unclear, recent safety concerns regarding paclitaxel DCBs including a risk of cytotoxicity and distal embolization have highlighted the need for an alternative cytostatic drug on DCBs.[20]

Despite the theory and established evidence from DES trials, our mechanistic randomized study has shown that the MagicTouch SCB is not noninferior to the SeQuent Please Neo PCB in terms of angiographic net lumen gain at 6 months. This difference is mainly caused by a significantly smaller LLL with PCB compared to SCB (0.00 vs 0.32; $P < 0.001$), with LLE at follow-up seen in 53.7% and 30.0% of lesions treated with PCB and SCB, respectively. Comparable findings were reported by Ahmad et al[12] among 70 patients with de novo coronary lesions randomized to

treatment with an SCB (SeQuent SCB, B. Braun; 4 mg/mm^2) or a PCB (SeQuent Please, B. Braun; 3 mg/mm^2) wherein LLE at the 6-month angiographic follow-up was detected in almost two-thirds of the lesions treated with a PCB and only about one-third of the lesions treated with an SCB—an incidence similar to the frequency of 20% to 30% reported for "plain old balloon angioplasty." In 4 serial cohorts of approximatively 100 vessels, Serruys et al[21] reported respective LLLs of −0.05 mm, 0.07 mm, 0.37 mm, and 0.41 mm at 1, 2, 3, and 4 months, with the absence of any further increases in LLL beyond this time suggesting that the proliferative and constrictive remodeling process was no longer active. The relationship between acute angiographic gain and LLL at the 6-month follow-up—adjusted for the covariates MLD and lesion location—was established from a pooled analysis of 3,078 patients and can be characterized by the linear regression.[22] In the present study, following SCB treatment, each millimeter gain in the luminal diameter is penalized by a loss of 0.72 mm, whereas the penalty was only 0.37 for PCBs.

The favorable LLL with PCBs could be explained by its specific pharmacokinetic properties; paclitaxel is lipophilic and rapidly crosses the cell membrane binding to microtubules, thus inhibiting cell division and migration and, therefore, cell proliferation.[18] Lipidic nanoparticle technologies have strived to enhance the bioresorption and retention of sirolimus released from the MagicTouch; however, whether this can compete with the superior tissue absorption and retention of paclitaxel remains to be seen.

The relationship between the LLL and acute dissection volume generated by predilatation pre-DCB treatment and quantified by OCT confirms that the coating formulation on the MagicTouch does not effectively prevent the restenotic process triggered by increasing barotrauma. The parietal concentration in sirolimus (0.118 ng/mg at 30 days in porcine model, presented by Aloke at TCT2022)[23] may be insufficient to inhibit the proliferative and constrictive remodeling processes occurring in the first 3 months following the barotrauma of the balloon angioplasty. Conversely, despite increasing barotrauma, the flat regression line between dissection volume and LLL following PCB demonstrates its efficacy in stifling the restenosis process.

Disappointing as these results are, we should not prematurely conclude that paclitaxel is intrinsically better than sirolimus for SVD but use this as a stimulus to further investigate the drug formulation (crystalline or amorphous), mechanism of absorption, kinetics of retention, depth of penetration, and duration of therapeutic cytostatic inhibition.[19] Of note, a DCB coated with Biolimus A9 (Biosensors Europe SA, Morges, Switzerland), which is 9 times less hydrophilic than sirolimus, was also recently shown to be inferior to paclitaxel (presented at EuroPCR 2023).[24] Further clinical evidence will confirm the absence (or presence) of a class effect in DCBs.

STUDY LIMITATIONS. Efficacy is generally measured by both mechanistic and clinical parameters. There was a considerable difference in binary restenosis between SCBs vs PCBs (33.9% vs 12.7%) but no difference in TLR in this small sample size. The following are the potential reasons for this:

1. The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial[25] has led interventionists to re-evaluate the intrinsic value and benefit of myocardial revascularization in chronic coronary syndrome patients, especially if the vessel subtends a small amount of myocardium at risk as in small vessel. An increasing number of patients are likely to be treated with pharmacologic therapy first, even if a significant (re)stenosis is present.
2. Functional assessment of coronary artery (re)stenoses plays a more crucial role in guiding the treatment decision making of patients with coronary artery disease than assessment by QCA %DS. According to QFR assessment, the target lesion/vessel with proven ischemia (QFR ≤0.80) was 13 (21.3%) and 5 (8.9) for SCBs and PCBs, respectively. Conversely, only 2 patients in the PCB group did not undergo repeat revascularization even if QFR ≤0.80, whereas in the SCB group, there were 8 patients. This might potentially represent a bias caused by the open-label nature of the study design.
3. The present study was not designed nor powered to demonstrate any relevant clinical outcomes. Therefore, it is not currently possible to forecast longer-term clinical outcomes from large ongoing RCTs comparing SCBs with PCBs.

Furthermore, in the design and in the trial planning a net gain at 6 months of 0.87 ± 0.51 mm was assumed according to the PEPCAD study[17] used for the power calculation and sample size. However, vessels with smaller RVD were enrolled in the TRANSFORM-I study compared to the PEPCAD study (2.05 mm vs 2.35 mm), which resulted in substantially less net gain than expected. Subsequently, the non-inferiority margin turned out to be generous. Furthermore, studies are warranted to determine the

efficacy of the SCB balloon in de novo lesions with SVD or large vessel disease.

CONCLUSIONS

This randomized mechanistic outcome study showed that the MagicTouch SCB failed to achieve noninferiority compared to the SeQuent Please Neo PCB for angiographic net gain at 6 months. Larger and longer-term studies powered for clinical outcomes are warranted to determine the efficacy of SCBs vs PCBs in de novo lesions.

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Dr Serruys reports consultancy for Merillife, Novartis, SMT (Sahajanand Medical technological), Philips/Volcano, and Xeltis, outside the submitted work. All other authors have no conflict of interest to declare.

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PERSPECTIVES

WHAT IS KNOWN? Clinical evidence of DCBs in treating de novo SVD is primarily based on studies of PCBs, putatively related to their favorable pharmacokinetic properties.

WHAT IS NEW? To date, data from randomized controlled trials on outcomes following treatment with SCBs are limited. Despite the theory and established evidence from DES trials, our mechanistic randomized study has shown that the MagicTouch SCB is not noninferior to the SeQuent Please Neo PCB in terms of angiographic net lumen gain at 6 months. The relationship between the LLL and acute dissection volume quantified by OCT supports that the coating formulation on the SCB does not effectively prevent the restenotic process triggered by increasing barotrauma.

WHAT IS NEXT? Larger and longer-term studies powered for clinical outcomes are warranted to determine the efficacy of SCB vs PCB and to confirm the absence (or presence) of a class effect in DCBs.

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KEY WORDS angiographic outcome, drug-coated balloon, paclitaxel, randomized controlled trial, sirolimus

APPENDIX For supplemental tables and figures, please see the online version of this paper.