CHRONIC TOTAL OCCLUSION

WILEY | *Journal Of* Interventional Cardiology

Impact of ultra-thin struts on restenosis after chronic total occlusion recanalization: Insights from the randomized PRISON IV trial

Carlo Zivelonghi MD[1,2] (ID) | Koen Teeuwen MD[3] |
Pierfrancesco Agostoni MD, PhD[1] | Renè J. van der Schaaf MD, PhD[4] |
Flavio Ribichini MD[2] | Tom Adriaenssens MD, PhD[5] |
Johannes C. Kelder MD, PhD[1] | Jan G. P. Tijssen PhD[6] |
José P. S. Henriques MD, PhD[6] | Maarten J. Suttorp MD, PhD, FESC[1]

[1] Department of Cardiology, Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands

[2] Department of Cardiology, University of Verona, Verona, Italy

[3] Department of Cardiology, Catharina Hospital, Eindhoven, The Netherlands

[4] Department of Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

[5] Department of Cardiology, University Hospital Leuven, Belgium

[6] Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
Maarten J. Suttorp, MD, PhD, FESC, Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands.
Email: m.suttorp@antoniusziekenhuis.nl

Objectives: The PRISON-IV trial showed inferior outcome in patients with chronic total occlusions (CTOs) treated with the ultrathin-struts (60 μm for stent diameter ≤3 mm, 81μm >3 mm) hybrid-sirolimus eluting stents (SES) compared with everolimus eluting stents (EES, 81 μm). The aim of this study is to investigate if the use of smaller stents (≤3 mm) was responsible for the inferior outcome reported in the trial.

Methods: In the PRISON-IV trial 330 patients with CTO lesion were randomized 1:1 to receive either hybrid-SES or EES. The hybrid-SES failed to reach the non-inferiority primary endpoint of in-segment late lumen loss (LLL) at 9-month angiographic follow-up. In this sub-analysis, we divided the population according to the different size of stents implanted in those receiving only stents with diameter ≤3 mm (Group-A, 178 patients), only stents >3 mm (Group-B, 59 patients), and those receiving stents of both sizes (Group-C, 93 patients).

Results: Baseline and procedural characteristics were comparable in the three groups. At angiographic follow-up, most of the adverse outcomes occurred in Group A, with higher incidence of binary restenosis in the Hybrid-SES versus EES (10.3% vs 1.3%, $P = 0.03$) and augmented in-stent diameter stenosis (26.04 ± 18.59% vs 21.24 ± 12.84, $P = 0.06$). Similarly, optical coherence tomography (OCT), which was performed in 60 patients at follow-up, documented a mild trend toward lower values of minimum in stent area in Hybrid-SES arm of Group A ($4.4 ± 1.02mm^2$ vs $5.0 ± 1.28mm^2$, respectively, $P = 0.16$).

Conclusions: The present analysis suggests that the inferior performance of the ultra-thin hybrid-SES in CTO-PCI is particularly pronounced when smaller stent (≤3 mm diameter) are adopted, if compared with EES.

KEYWORDS
chronic total occlusions, drug-eluting stents, ultrathin struts

1 | INTRODUCTION

Procedural success rates in percutaneous treatment of coronary chronic total occlusions (CTOs) have certainly improved in the last years,[1,2] with continuous benefits deriving from developments in materials, devices, and techniques. The clinical advantages of a full coronary revascularization by means of CTO recanalization, as shown in some reports, may lead to improved long-term survival in patients presenting with both stable coronary artery disease (CAD) and acute coronary syndrome (ACS).[3–5] In addition, the long-term incidence of cardiac adverse events resulted higher in this population than in patients presenting with non-CTO lesions.[6–8] On the other hand, CTOs often present adverse plaque characteristics (eg, large calcium deposit, superior lesion length, diffuse disease upstream, and downstream the CTO lesion itself) challenging the performance of currently available devices, even in the era of second-generation drug eluting stents (DES). Moreover, unconventional approaches (including all sub-intimal techniques) are commonly adopted to create a functional but not physiological lumen to the distal vessel, thus creating an additionally unfavorable premise for long-term clinical success.[9] In these settings, all DES features (ranging from strut thickness and composition to the polymer and drug eluted) are involved in the procedural and clinical success, as already demonstrated in the past for regular percutaneous coronary intervention (PCI).[10–13] In the PRISON IV randomized multicentre trial, successfully reanalysed CTO lesions were randomly allocated in a 1:1 fashion to stent implantation with Orsiro, a hybrid ultrathin-strut sirolimus-eluting stent (SES, Biotronik, Berlin, Germany) or Xience, a thin-strut (81 μm) everolimus-eluting stents (EES, Abbott Vascular, Santa Clara, CA).[14] The SES study device did not meet the primary non-inferiority endpoint of in-segment late lumen loss (LLL) estimated by Quantitative Coronary Analysis (QCA) at 8 month of angiographic follow-up, mainly because of an increased rate of focal in-stent restenosis in the SES group. The aim of the present analysis is to investigate the role of the "real" ultrathin-struts SES (Orsiro with diameter ≤3 mm) in the less favorable angiographic outcome described for this device in the PRISON IV trial.

2 | METHODS

This is a sub-analysis from the PRISON IV multicentre trial, whose design, major inclusion and exclusion criteria, endpoints, definitions, and results have been previously described in detail (NCT01516723).[2,14] Briefly, after successful recanalization of native total or chronic total coronary occlusions, 330 patients were randomized in a 1:1 fashion to receive either a hybrid Orsiro SES or the Xience Prime/Xpedition EES. Of note, the SES consists of a cobalt-chromium platform covered with a biodegradable polymer, made of ultrathin 60 μm struts for stent diameters ≤3 mm and 80 μm struts for diameter >3 mm, as indicated by the manufacturers. On the other hand, the EES with durable polymer presents a cobalt-chromium platform with a strut thickness of 81 μm. Procedural and technical choices were left to the operator's discretion, and included both femoral and radial approaches as well as antegrade and retrograde techniques. All patients received dual antiplatelet therapy prior to the procedure with the indication to maintain it for at least 12 months. Clinical follow-up was scheduled at 1, 6, 9, and 12 months. Angiographic follow-up was mandatory at 9 months.

In the present analysis, we investigated the hypothesis that the thinner struts platform of the SES with diameter ≤3 mm may have been responsible for the inferior angiographic outcome observed in the Prison IV trial. For this reason, patients were further divided according to the diameter size of the stent received into the following groups: Group A (n = 178), patients receiving only stents with diameter ≤3 mm; Group B (n = 59), patients receiving only stents with diameter >3 mm; Group C (n = 93), patients receiving both stents with diameter >3 and ≤3 mm.

Endpoints of this analysis included angiographic outcomes as in-stent LLS, MLD, in-stent percentage of diameter stenosis, binary restenosis, and re-occlusions at 8 months. Moreover, data regarding lumen and stent areas as assessed with optical coherence tomography (OCT) were included to support the angiographic findings.

QCA was assessed offline in an independent angiographic core laboratory (St. Antonius Hospital Angiographic Core Laboratory, Nieuwegein, the Netherlands) with automatic edge detection software CMS version 5.3 (Medis Medical Imaging Systems, Leiden, the Netherlands), by experienced personnel blinded to clinical information and allocated stent. QCA measures included the proximal-edge, distal-edge and in-stent diameters of the reference vessel (RVD), the minimal luminal diameters (MLD), percentages of diameter stenosis (difference between RVD and MLD/RVD × 100), and LLL (difference between MLD after the procedure and MLD at follow-up). Binary restenosis was defined as a diameter stenosis >50% inside the stented segment at angiographic follow-up.

The full OCT analysis, methodology and results have been described previously.[15] Briefly, 30 patients were assessed with OCT during the 9-month follow-up procedure in both groups. All images were recorded with a frequency domain OCT imaging system (C7XR™ or OPTIS™ OCT imaging system; St. Jude Medical, St. Paul, MN). OCT analyses were performed offline by the local core laboratory (University Hospital Leuven, Leuven, Belgium) in a blinded fashion. Quantitative strut level analysis was performed every third frame (0.6 mm interval) along the entire target segment. A dedicated automated software system developed at the Leuven Medical Imaging Centre was used for quantitative OCT analysis.[16] The OCT measurements included mean and minimum lumen area, together with stent mean, minimum and maximum area.

Baseline and outcome data were analysed using descriptive statistics. Numerical values were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Categorical variables were expressed as percentages. Comparisons between groups were performed using Pearson chi-square test for categorical variables and student t-test for continuous variables. A two tailed probability value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPPS version 22.0 (SPSS, Inc., Chicago, IL).

TABLE 1 Demographic characteristics in the three groups of the study population

	Small stents (n = 178)			Large stents (n = 59)			Both (n = 93)		
	SES (n = 92)	EES (n = 86)	P-value	SES (n =)	EES (n =)	P-value	SES (n = 43)	EES (n = 50)	P-value
Age	63 ± 9	62 ± 10	0.68	62 ± 11	63 ± 10	0.76	63 ± 10	62 ± 11	0.71
Male sex	60 (65%)	66 (77%)	0.1	28 (93.3%)	25 (86.2%)	0.42	34 (79.1%)	46 (92%)	0.13
Smoking			0.37			0.21			0.69
Never	38 (41.8%)	26 (31%)		11 (36.7%)	5 (17.2%)		11 (26.2%)	16 (32.7%)	
Stopped >6 weeks	31 (34.1%)	29 (34.5%)		9 (30%)	12 (41.4%)		14 (33.3%)	15 (30.6%)	
Current	22 (24.2%)	29 (34.5%)		10 (33.3%)	12 (41.4%)		17 (40.5%)	18 (36.7%)	
Diabetes			0.91			0.29			0.68
Non-insulin dependent	14 (15%)	14 (16%)		3 (10%)	6 (20.7%)		11 (25.6%)	11 (22%)	
Insulin-dependent	3 (3.3%)	2 (2.4%)		0	1 (3.4%)		0	0	
Dyslipidemia	62 (67.4%)	57 (66.3%)	0.59	19 (63.3%)	17 (58.6%)	0.1	27 (62.8%)	29 (58%)	0.62
Hypertension	47 (51%)	55 (64%)	0.16	18 (60%)	17 (58.6%)	0.91	21 (48.8%)	26 (52%)	0.59
Family history	42 (45.7%)	49 (57.6%)	0.17	14 (46.7%)	17 (58.6%)	0.62	23 (53.5%)	21 (42%)	0.4
Renal impairment (GFR)[a]			0.3			0.51			0.26
Normal (>60)	80 (92%)	65 (84.4%)		22 (84.6%)	25 (89.3%)		34 (89.5%)	45 (95.7%)	
Mild (45–59)	5 (5.7%)	8 (10.4%)		3 (11.5%)	2 (7.1%)		4 (10.5%)	2 (4.3%)	
Moderate (30–44)	2 (2.3%)	2 (2.6%)		0	1 (3.6%)		0	0	
Severe (<30)	0	2 (2.6%)		1 (3.8%)	0		0	0	
Left ventricle ejection fraction			0.07			0.32			0.37
>50%	85 (92.4%)	70 (81.4%)		24 (80%)	26 (89%)		35 (81%)	43 (86%)	
30-50%	7 (7.6%)	12 (14%)		6 (20%)	3 (10.3%)		4 (9.3%)	6 (12%)	
<30%	0	4 (4.7%)		0	0		4 (9.3%)	1 (2%)	
History									
Previous myocardial infarction	27 (29.3%)	26 (30.2%)	0.38	11 (36.7%)	7 (24.1%)	0.37	14 (32.6%)	15 (30%)	0.28
Previous coronary-artery by-pass graft	3 (3.3%)	5 (5.8%)	0.48	1 (3.3%)	2 (6.9%)	0.61	2 (4.7%)	4 (8%)	0.68
Previous ercutaneous coronary intervention	28 (30.4%)	24 (27.9%)	0.74	4 (13.3%)	7 (24.1%)	0.33	15 (34.9%)	19 (38%)	0.83
Previous stroke	5 (5.4%)	7 (8.2%)	0.43	5 (16.7%)	3 (10.3%)	0.7	3 (7%)	1 (2%)	0.49

[a]Glomerular Filtration Rate (mL/min/1.73 m^2).

TABLE 2 Angiographic and procedural features in the three groups of the study population

	Small stents			Large stents			Both		
	SES (n = 92)	EES (n = 86)	P-value	SES (n = 30)	EES (n = 29)	P-value	SES (n = 43)	EES (n = 50)	P-value
Occluded vessel			0.24			0.86			0.79
Right coronary artery	40 (43.5%)	27 (31.4%)		21 (70%)	22 (75.9%)		33 (76.7%)	38 (76%)	
Left anterior descendant	32 (34.8%)	35 (40.7%)		8 (26.7%)	6 (20.7%)		8 (18.6%)	8 (16%)	
Left circumflex	20 (21.7%)	24 (27.9%)		1 (3.3%)	1 (3.4%)		2 (4.7%)	3 (6%)	
Collateral filling	88 (95.7%)	84 (97.7%)	0.68	28 (93.3%)	28 (96.6%)	0.61	41 (95.1%)	47 (94%)	0.89
Bridge collaterals	43 (46.7%)	36 (41.9%)	0.55	13 (43.3%)	14 (48.3%)	0.79	17 (39.5%)	20 (40%)	0.55
Retrograde collaterals	82 (89.1%)	75 (87.2%)	0.81	28 (93.3%)	29 (100%)	0.49	42 (97.7%)	48 (96%)	0.24
Catheter size			0.53			0.34			0.27
5	2 (2.2%)	5 (5.8%)		0	0		0	0	
6	83 (90.2%)	75 (87.2%)		29 (96.7%)	26 (89.7%)		39 (92.9%)	44 (88%)	
7	5 (5.4%)	3 (3.5%)		1 (3.3%)	1 (3.4%)		1 (2.4%)	5 (10%)	
8	2 (2.2%)	3 (3.5%)		0	2 (6.9%)		2 (4.8%)	1 (2%)	
Vascular access			0.74			0.21			0.37
Single access									
Femoral	41 (44.6%)	44 (51.2%)		15 (50%)	11 (37.9%)		7 (16.3%)	10 (20%)	
Radial	31 (33.7%)	26 (30.2%)		7 (23.3%)	12 (41.4%)		13 (30.2%)	13 (26%)	
Double access									
Radial/femoral	10 (10.9%)	10 (11.6%)		7 (23.3%)	3 (10.3%)		20 (46.5%)	18 (36%)	
Femoral/femoral	9 (9.8%)	6 (7%)		1 (3.3%)	3 (10.3%)		3 (7%)	9 (18%)	
Radial/radial	1 (1.1%)	0		0	0		1 (0.6%)	0	
Recanalization technique			0.73			0.53			0.88
Antegrade wire escalation									
Single wire	79 (86.8%)	77 (90.6%)		26 (86.7%)	26 (89.7%)		27 (64.3%)	31 (62%)	
Parallel wire	3 (3.3%)	4 (4.7%)		0	0		3 (7.1%)	5 (10%)	
Antegrade dissection re-entry									
Mini STAR/LAST	1 (1.1%)	0		0	0		1 (2.4%)	0	
Crossboss/stingray	1 (1.1%)	0		0	0		2 (4.8%)	1 (2%)	
Retrograde									
Retrograde wire escalation	4 (4.4%)	2 (2.4%)		3 (10%)	2 (6.9%)		4 (9.5%)	5 (10%)	
Kissing wire	2 (2.2%)	2 (2.4%)		1 (3.3%)	0		1 (2.4%)	1 (2%)	
Reverse CART	1 (1.1%)	0		0	1 (3.4%)		4 (9.5%)	7 (14%)	
Primary approach			0.57			0.99			0.99
Antegrade	84 (91.3%)	81 (94.2%)		26 (86.7%)	26 (89.7%)		31 (72.1%)	37 (74%)	
Retrograde	8 (8.7%)	5 (5.8%)		4 (13.3%)	3 (10.3%)		12 (27.9%)	13 (26%)	
Japanese-chronic total occlusion score									
Mean[a]	1.6 ± 1	1.7 ± 1	0.37	1.9 ± 1.3	2.3 ± 1.1	0.27	2 ± 1.1	2.4 ± 1.1	0.09
Risk group			0.13			0.77			0.37
0 (Easy)	13 (14.1%)	5 (5.8%)		4 (13.3%)	1 (3.4%)		3 (7%)	2 (4%)	
1 (Intermediate)	31 (33.7%)	36 (41.9%)		8 (26.7%)	6 (20.7%)		13 (30.2%)	7 (14%)	
2 (Difficult)	31 (33.7%)	24 (27.9%)		8 (26.7%)	10 (34.5%)		11 (25.6%)	18 (36%)	
≥3 (Very difficult)	17 (18.4%)	21 (24.5%)		10 (33.3%)	12 (41.3%)		16 (37.2%)	23 (46%)	
Variables									
Blunt stump	32 (34.8%)	39 (45.3%)	0.17	14 (46.7%)	17 (58.6%)	0.44	17 (39.5%)	32 (64%)	0.02
Calcification	56 (60.9%)	53 (61.3%)	0.99	18 (60%)	19 (65.5%)	0.79	29 (67.4%)	38 (76%)	0.49

(Continues)

TABLE 2 (Continued)

	Small stents			Large stents			Both		
	SES (n = 92)	EES (n = 86)	P-value	SES (n = 30)	EES (n = 29)	P-value	SES (n = 43)	EES (n = 50)	P-value
Bending	8 (8.7%)	8 (9.3%)	0.99	9 (30%)	14 (48.3%)	0.18	13 (32.6%)	12 (24%)	0.48
Lenght	39 (42.4%)	41 (47.7%)	0.55	15 (50%)	15 (51.7%)	0.99	23 (53.5%)	24 (48%)	0.68
Re-try	1 (1.1%)	1 (1.2%)	0.99	0	0	NA	0	1 (2%)	0.99
Stent diameter[a]	2.87 ± 0.21	2.83 ± 0.24	0.19	3.69 ± 0.24	3.65 ± 0.23	0.56	3.54 ± 0.18	3.55 ± 0.15	0.92
Stent balloon pressure[a]	14.6 ± 3	14.9 ± 3.1	0.49	14.7 ± 3.6	14.5 ± 3.1	0.86	15.6 ± 2.9	15.1 ± 3.1	0.47
Post-dilation	27 (29.3%)	34 (39.5%)	0.16	12 (40%)	9 (31%)	0.59	18 (41.9%)	15 (30%)	0.28
Non-compliant balloon	23 (85.2%)	26 (74.3%)	0.47	10 (83.3%)	8 (88.9%)	0.99	15 (83.3%)	12 (80%)	0.99
Post-dilation diameter[a]	3.15 ± 0.37	3.14 ± 0.36	0.92	3.98 ± 0.6	3.89 ± 0.41	0.69	3.72 ± 0.3	3.6 ± 03	0.28
Post-dilation pressure[a]	18 ± 4.2	18 ± 4.1	0.97	19.1 ± 4.3	21.7 ± 4.2	0.2	18.5 ± 4.9	20.1 ± 2.8	0.28
Total stent lenght[a]	45 ± 21	40 ± 20	0.12	41 ± 22	39 ± 16	0.63	73 ± 24	81 ± 24	0.16
Number of stents[a]	1.76 ± 0.8	1.67 ± 0.8	0.47	1.66 ± 0.8	1.41 ± 0.5	0.17	2.88 ± 1.07	2.82 ± 0.85	0.75
TIMI-flow final			0.37			1			0.99
0	0	1 (1.2%)		0	0		0	0	
1	0	0		0	0		0	0	
2	1 (1.1%)	0		0	0		1 (2.3%)	1 (2%)	
3	91 (98.9%)	85 (98.8%)		29 (100%)	30 (100%)		42 (97.7)	49 (98%)	

[a]Mean ± SD.

3 | RESULTS

Demographic data between the two devices were evenly distributed in the three sub-groups (see Table 1). Of note, left ventricle ejection fraction (LVEF) showed a trend toward worse values in the EES cohort of Group A (7.6% vs 18.7% of patients with LVEF <50%, P = 0.07). Similarly, angiographic baseline characteristics were comparable in the two treatment arms of all three sub-groups (see Table 2). The only significant difference was noted in Group C, where coronary lesions in the EES group showed a proximal blunt stump more frequently than in the SES group (64% vs 39.5%, respectively, P = 0.02), with a mean J-CTO score broadly comparable (2.4 ± 1.1 vs 2 ± 1.1, respectively, P = 0.09). The prevalence of calcified pattern in the CTO lesion was high (from 60% to 76%) and comparable in all the groups. The most successful recanalization technique was antegrade wire escalation (AWE) in all sub-groups without significant differences between the treatment arms; however in Group C a trend toward more common adoption of retrograde techniques can be observed, resulting in broadly longer stented segments if compared with the two remaining groups (see Table 2). Consistently with the sub-groups division, the mean stent diameter was 2.85 ± 0.22 mm in Group A, 3.67 ± 0.24 mm in Group B, and 3.55 ± 0.16 mm in Group C, without significant differences between the two treatment cohorts.

Complete QCA results for all the study groups are listed in Table 3. In Group A, post-procedural in-stent RVD, MLD, and DS were similar in the SES and EES group. At 9 month follow-up, the proximal and distal RVDs increased in both treatment groups (P = ns), while in-stent RVD remained stable. In-stent MLD showed a trend toward lower values in the SES group when compared with the EES group (2.06 ± 0.61 mm vs 2.21 ± 0.48 mm, P = 0.08), with a strong tendency to higher in-stent DS (26.04 ± 18.59% and 21.24 ± 12.84%, respectively, P = 0.06), and a similar in-stent LLL. The binary restenosis rate, however, was significantly higher in the SES group: 8 (10.3%) versus 1 (1.3%), P = 0.03.

In Group B reference diameters after PCI were similar and higher than in Group-A, reflecting the mean stent diameter implanted in this population, with also similar in-stent MLD and DS. At 9 month follow-up, all RVDs slightly increased in both treatment groups (P = ns), with comparable in-stent MLD and DS. In addition, in-stent LLL resulted low and comparable in the two cohorts (0.03 ± 0.78 mm vs 0.02 ± 0.41, respectively, P = 0.97), as was the incidence of binary restenosis.

In Group C, reference diameters after PCI were higher in the SES arm (proximal RVD 3.65 ± 0.49 mm and 3.46 ± 0.37 mm, respectively, P = 0.04), showing a significantly higher proximal percentage DS in the same population (8.25 ± 10.70% vs 2.12 ± 8.62%, respectively, P = 0.003). On the other hand, similar in-stent RVD and in-stent DS were observed. At 9 month follow-up, proximal RVD was significantly higher in the SES group (3.78 ± 0.55 mm vs 3.56 ± 0.40 mm, P = 0.05), while in-stent MLD, in-stent LLL, and the incidence of binary restenosis were comparable in the two cohorts (Figure 1).

A complete list of OCT results for the three study groups is shown in Table 4. In Group A, mean lumen area and minimum lumen area were very similar in both study arms. Broadly lower values, although statistically non-significant, were observed for minimum stent area and mean stent area in the SES group (4.4 ± 1.02 mm^2 vs 5.0 ± 1.28 mm^2 and 5.28 ± 1.05 mm^2 vs 6.1 ± 1.36 mm^2, respectively).

In Group B, measurements of lumen minimal and mean area were similar in SES and EES. Stent mean, minimal and maximum area were also not significantly different between the two study arms, but of

TABLE 3 Quantitative Coronary Analysis (QCA) results in the three groups of the study population

	Small stents (n = 178)			Large stents (n = 59)			Both (n = 93)		
	SES (n = 92)	EES (n = = 86)	P-value	SES (n = 30)	EES (n = 29)	P-value	SES (n = 43)	EES (n = 50)	P-value
Pre-procedure									
Occlusion lenght	19.3 ± 12.6	18.7 ± 9.8	0.76	20.8 ± 9.1	19.9 ± 8.9	0.74	22.4 ± 13.8	25.1 ± 21.6	0.49
Proximal RVD	2.44 ± 0.87	2.57 ± 0.93	0.32	2.71 ± 0.88	2.96 ± 1	0.33	2.68 ± 1.24	2.52 ± 1.22	0.54
Post-procedure									
Proximal RVD	2.96 ± 0.35	2.97 ± 0.37	0.81	3.71 ± 0.49	3.70 ± 0.47	0.99	3.65 ± 0.49	3.46 ± 0.37	0.04
Proximal Edge RVD	2.92 ± 0.35	2.93 ± 0.37	0.9	3.66 ± 0.47	3.63 ± 0.43	0.84	3.61 ± 0.48	3.44 ± 0.37	0.06
Proximal Edge MLD	2.77 ± 0.42	2.76 ± 0.37	0.9	3.55 ± 0.53	3.52 ± 0.45	0.78	3.29 ± 0.44	3.36 ± 0.45	0.45
Proximal DS%	4.98 ± 8.92	5.23 ± 8.27	0.85	2.69 ± 9.6	3.17 ± 6.02	0.82	8.25 ± 10.70	2.12 ± 8.62	0.003
Distal RVD	2.28 ± 0.38	2.26 ± 0.42	0.77	3.02 ± 0.31	2.97 ± 0.36	0.56	2.48 ± 0.41	2.45 ± 0.36	0.74
Distal Edge RVD	2.33 ± 0.36	2.32 ± 0.39	0.88	3.07 ± 0.3	3.03 ± 0.36	0.66	2.54 ± 0.4	2.51 ± 0.34	0.69
Distal Edge MLD	2.28 ± 0.39	2.30 ± 0.38	0.78	3.05 ± 0.33	3.01 ± 0.41	0.72	2.52 ± 0.4	2.48 ± 0.33	0.65
Distal DS %	2.01 ± 9	0.58 ± 10.01	0.32	0.71 ± 5.07	0.47 ± 8.78	0.89	0.35 ± 9.66	0.66 ± 8.3	0.87
In-stent RVD	2.73 ± 0.35	2.71 ± 0.4	0.81	3.4 ± 0.38	3.36 ± 0.38	0.71	3.16 ± 0.58	2.97 ± 0.38	0.07
In-stent MLD	2.24 ± 0.33	2.23 ± 0.36	0.74	2.81 ± 0.37	2.81 ± 0.24	0.98	2.43 ± 0.42	2.36 ± 0.41	0.43
In-stent DS%	17.54 ± 7.49	17.75 ± 7.15	0.85	17.23 ± 7.19	16 ± 5.91	0.48	22.79 ± 6.97	20.92 ± 7.11	0.21
9-month follow-up									
Proximal RVD	3.04 ± 0.35	3.1 ± 0.46	0.34	3.88 ± 0.54	3.73 ± 0.59	0.35	3.78 ± 0.55	3.56 ± 0.40	0.05
Proximal Edge RVD	2.93 ± 0.59	3.01 ± 0.57	0.39	3.67 ± 0.93	3.7 ± 0.57	0.91	3.75 ± 0.55	3.47 ± 0.68	0.06
Proximal Edge MLD	2.78 ± 0.6	2.86 ± 0.59	0.4	3.38 ± 0.97	3.52 ± 0.66	0.55	3.6 ± 0.55	3.37 ± 0.75	0.13
Proximal DS%	5.05 ± 7.8	4.78 ± 11.01	0.86	7.86 ± 9.47	4.78 ± 9.61	0.25	3.63 ± 8.15	2.84 ± 10.12	0.71
Distal RVD	2.36 ± 0.39	2.44 ± 0.42	0.26	3.26 ± 0.46	3.33 ± 0.82	0.73	2.71 ± 0.35	2.64 ± 0.42	0.4
Distal Edge RVD	2.37 ± 0.51	2.45 ± 0.49	0.29	3.19 ± 0.79	3.36 ± 0.78	0.47	2.76 ± 0.34	2.63 ± 0.57	0.23
Distal Edge MLD	2.33 ± 0.54	2.41 ± 0.52	0.32	3.11 ± 0.81	3.2 ± 0.58	0.65	2.73 ± 0.38	2.57 ± 0.59	0.17
Distal DS %	1.43 ± 8.61	1.38 ± 9.04	0.97	2.43 ± 6.51	2.98 ± 12.3	0.84	1.23 ± 8.04	1.99 ± 11.78	0.75
In-stent RVD	2.69 ± 0.58	2.76 ± 0.51	0.4	3.51 ± 0.86	3.6 ± 0.69	0.67	3.2 ± 0.44	3.03 ± 0.66	0.22
In-stent MLD	2.06 ± 0.61	2.21 ± 0.48	0.08	2.76 ± 0.79	2.79 ± 0.46	0.86	2.44 ± 0.4	2.23 ± 0.62	0.1
In-stent DS%	26.04 ± 18.59	21.24 ± 12.84	0.06	24.30 ± 19.54	21.55 ± 11.32	0.54	23.43 ± 9.83	28.54 ± 15.05	0.09
In-stent LLL	0.19 ± 0.60	0.05 ± 0.42	0.1	0.03 ± 0.78	0.02 ± 0.41	0.97	0.01 ± 0.32	0.15 ± 0.55	0.19
In-stent binary restenosis	8 (10.3%)	1 (1.3%)	0.03	2 (8%)	0	0.23	1 (2.9%)	2 (4.8%)	0.99
Re-occlusion	2 (2.2%)	1 (1.2%)	0.99	1 (3.3%)	0	0.99	0	1 (2%)	0.99

note, SES values tended to be higher than those in the EES arm. Similar findings were reported in Group C.

4 | DISCUSSION

The ultrathin struts (60 μm) of the hybrid SES were designed to limit the arterial injury and amount of metallic-body placed with stent implantation, thus hindering two possible mechanisms responsible for restenosis. The present sub-analysis from the PRISON IV trial suggests that the relatively inferior performance of this device is confirmed when smaller stents (≤3 mm in diameter) are adopted, which indeed consist of those with the ultra-thin struts. In fact, in this population (Group A), despite similar baseline patients characteristics and comparable angiographic (eg, J-CTO score) and procedural (stent

diameter and inflation pressure, post-dilation, use of NC-balloons) features, the follow-up QCA disclosed a strong trend toward higher in-stent DS (26.04 ± 18.59% vs 21.24 ± 12.84%, P = 0.06) and a statistically significant, nearly eightfold higher, incidence of binary-restenosis (P = 0.03). A possible explanation for these observations could be the reduced radial strength offered by the ultra-thin struts devices, as potentially supported by the OCT analysis, which showed a mild trend toward lower stent area values in this group. An alternative explanation could be identified in a lower neo-intimal inhibition operated by the hybrid SES, with more pronounced effects in vessel with smaller diameter. Indeed, these findings were not confirmed in the population receiving larger stents (>3 mm in diameter, Group B), where the SES struts thickness is equal to 80 μm (as that of all EES stents), despite the low number of patients included in this group poses relevant limitations in drawing firm conclusions. In fact, similar
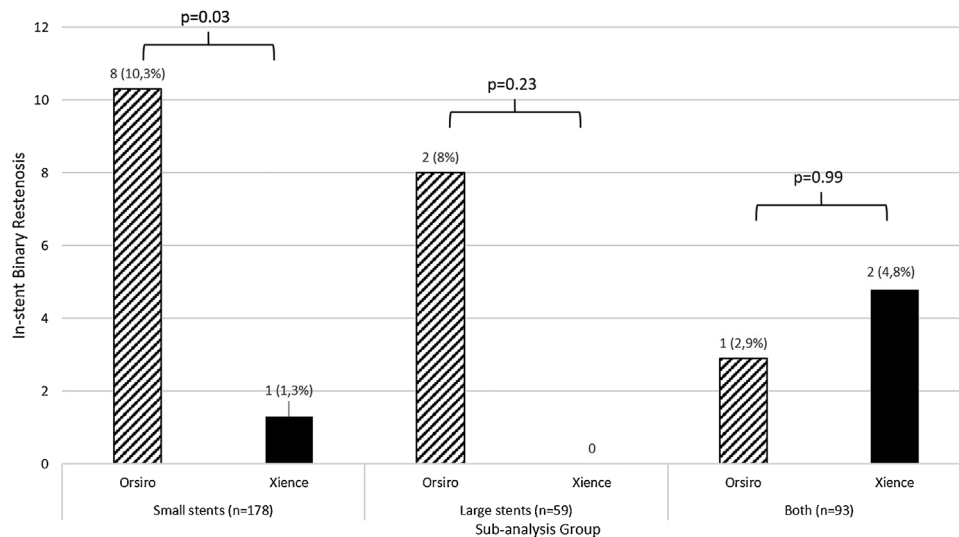
FIGURE 1 Incidence of binary restenosis in the two cohorts of treatment stratified in the three groups of analysis

evolutions in RVDs were observed in the two groups between post-procedural analysis and follow-up, without any increase in in-stent LLL or binary restenosis rate, which, on the contrary, resulted similar to those of the EES cohort in Group A. Consistent findings were observed in the OCT analysis, with stent area values substantially identical in the two groups. Finally, findings from the hybrid Group C, where stent of both sizes (≤3 and >3 mm) were used, are unavoidably less clearly oriented. In this group, the total stent length resulted higher than in the other two groups, with need for more stents implanted (see Table 2). The common adoption of different number of both stent sizes (small and large), with the respective different lengths, makes the two cohorts of this group highly heterogeneous and thus not appropriate for clear interpretation.

In the settings of complex coronary lesions, such as CTOs, the benefits of the ultra-thin struts in terms of reduced vascular injury and thrombogenicity are possibly counterpartied by an inferior vessel-wall supportive strength. The high prevalence of calcified lesions (ranging from 60% to 76% of patients in the different cohorts) and a generally greater lesion length (more than 20 mm in almost 50% of cases) could

be possible elements hindering the performance of the ultra-thin struts SES in the present settings. However, larger and dedicated trials are needed to confirm our findings.

5 | LIMITATIONS

Data presented in this sub-analysis derived from the randomized Prison IV trial, which makes our findings solid. However, some limitations must be acknowledged. First, the study was not designed to assess angiographic differences in the sub-group of patients receiving stent with diameter ≤3 mm. Second, QCA results, although clearly oriented, especially in Group A, are limited by the absolute low number of patients analysed in the cohort. Third, the clinical implications of these findings were not investigated in this sub-analysis, thus caution should be used before translating our results into clinical indications. In addition, the OCT analysis was carried out in an exploratory way, without mandatory assessments in the two groups of treatment, with consequent limited number of

TABLE 4 Optical coherence tomography findings in the three groups of the study population

	Small stents (n = 39)			Large stents (n = 11)			Both (n = 10)		
	SES (n = 17)	EES (n = 22)	P-value	SES (n = 7)	EES (n = 4)	P-value	SES (n = 6)	EES (n = 4)	P-value
Lumen Measurements									
Mean lumen area (mm²)[a]	5.8 ± 1.28	5.8 ± 1.39	0.92	9.0 ± 2.91	8.7 ± 0.97	0.77	8.5 ± 2.36	7.3 ± 1.06	0.45
Minimum lumen area (mm²)[a]	3.7 ± 1.45	4.0 ± 1.37	0.72	7.1 ± 2.3	6.8 ± 0.9	0.64	4.9 ± 0.99	4.3 ± 0.56	0.45
Stent Measurements									
Mean stent area (mm²)[a]	5.8 ± 1.05	6.1 ± 1.36	0.26	8.9 ± 2.44	8.8 ± 0.91	0.92	8.1 ± 1.65	8.0 ± 1.67	1
Minimum stent area (mm²)[a]	4.4 ± 1.02	5.0 ± 1.28	0.16	7.6 ± 2.06	7.4 ± 1.0.6	0.92	5.5 ± 0.87	5.4 ± 0.95	0.91
Maximum stent area (mm²)[a]	7.2 ± 1.52	7.5 ± 1.7	0.33	11.1 ± 2.42	10.5 ± 1.17	1	11.1 ± 3.32	11.2 ± 1.45	0.91

[a]Mean ± standard deviation.

examinations available. Finally, OCT analysis was performed only during the 9-month follow-up procedure, thus comparison with basal post-procedural results was not possible.

CONFLICTS OF INTEREST

All authors meet the authorship criteria, take full responsibility for all aspects of the reliability and freedom from bias of the data presented, and their discussed interpretation. The authors report no financial relationships or conflict of interest regarding the content herein.

ORCID

Carlo Zivelonghi (iD) http://orcid.org/0000-0001-9825-6589

REFERENCES

1. Maeremans J, Walsh S, Knaapen P, et al. The hybrid algorithm for treating chronic total occlusions in Europe: the RECHARGE registry. *J Am Coll Cardiol*. 2016;68:1958–1970.
2. Teeuwen K, van der Schaaf RJ, Adriaenssens T, et al. Randomized multicenter trial investigating angiographic outcomes of hybrid sirolimus-eluting stents with biodegradable polymer compared with everolimus-eluting stents with durable polymer in chronic total occlusions: the PRISON IV trial. *JACC Cardiovasc Interv*. 2017;10:133–143.
3. Mehran R, Claessen BE, Godino C, et al. Multinational chronic total occlusion registry. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. *JACC Cardiovasc Interv*. 2011;4:952–961.
4. Jones DA, Weerackody R, Rathod K, et al. Successful recanalization of chronic total occlusions is associated with improved long-term survival. *JACC Cardiovasc Interv*. 2012;5:380–388.
5. Valenti R, Migliorini A, Signorini U, et al. Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. *Eur Heart J*. 2008;29:2336–2342.
6. Taniwaki M, Stefanini GG, Silber S, et al. 4-year clinical outcomes and predictors of repeat revascularization in patients treated with new-generation drug-eluting stents: a report from the RESOLUTE all-comers trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). *J Am Coll Cardiol*. 2014;63: 1617–1625.
7. Yeh RW, Silber S, Chen L, et al. 5-year safety and efficacy of resolute zotarolimus-eluting stent: the RESOLUTE global clinical trial program. *JACC Cardiovasc Interv*. 2017;10:247–254.
8. Di Mario C, Serruys PW, Silber S, et al. Long-term outcomes after Resolute zotarolimus-eluting stent implantation in patients with ST-segment elevation acute myocardial infarction: insights from the RESOLUTE All Comers Trial and the RESOLUTE Global Clinical Trial Program. *EuroIntervention*. 2016;12:1207–1214.
9. Hasegawa K, Tsuchikane E, Okamura A, et al. Incidence and impact on midterm outcome of intimal versus subintimal tracking with both antegrade and retrograde approaches in patients with successful recanalisation of chronic total occlusions: J-PROCTOR 2 study. *EuroIntervention*. 2017;12:e1868–e1873.
10. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation*. 2001;103:2816–2821.
11. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. *J Am Coll Cardiol*. 2003;41:1283–1288.
12. Smits PC, Vlachojannis GJ, McFadden EP, et al. Final 5-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice: the COMPARE trial (a trial of everolimus-eluting stents and paclitaxel stents for coronary revascularization in daily practice). *JACC Cardiovasc Interv*. 2015;8:1157–1165.
13. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med*. 2010;362:1663–1674.
14. Teeuwen K, Adriaenssens T, Van den Branden BJ, et al. A randomized multicenter comparison of hybrid sirolimus-eluting stents with bioresorbable polymer versus everolimus-eluting stents with durable polymer in total coronary occlusion: rationale and design of the primary stenting of occluded native coronary arteries IV study. *Trials*. 2012;13:240.
15. Teeuwen K, Spoormans EM, Bennett J, et al. Optical coherence tomography findings: insights from the "randomised multicentre trial investigating angiographic outcomes of hybrid sirolimus-eluting stents with biodegradable polymer compared with everolimus-eluting stents with durable polymer in chronic total occlusions" (PRISON IV) trial. *EuroIntervention*. 2017;13:e522–e530.
16. Ughi GJ, Adriaenssens T, Onsea K, et al. Automatic segmentation of in-vivo intra-coronary optical coherence tomography images to assess stent strut apposition and coverage. *Int J Cardiovasc Imaging* 2012;28: 229–241.