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Reviews

The Orsiro Ultrathin, Bioresorbable-Polymer Sirolimus-Eluting Stent: A Review of Current Evidence

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ABSTRACT

Advances in stent design and the development of bioresorbable polymers have allowed the development of novel stent technologies such as the Orsiro bioresorbable-polymer sirolimus eluting stent (BP-SES). Over several non-inferiority trials, the BP-SES has demonstrated itself to be a safe and effective therapy for obstructive coronary artery disease. This article reviews the current evidence of the efficacy of the BP-SES and examines its performance in high-risk populations, such as patients presenting with ST-segment myocardial infarction, chronic total occlusions, diabetes, and small vessel disease.

1. Introduction

In recent years, a series of advances in stent technology has led to steady improvements in rates of restenosis and stent thrombosis and has reduced the need for repeat revascularization. The development of ultrathin struts, improvements in polymer biocompatibility, and the development of bioresorbable polymers have all aimed to decrease early stent thrombosis and reduce local inflammatory and hypersensitivity reactions, leading to reduced rates of in-stent restenosis, need for revascularization, and lower incidence of other adverse clinical events [1]. Biodegradable-polymer stents were designed to allow the steady and controlled eluting of antiproliferative drugs in the early phases of treatment. This mitigates neointimal hyperplasia [2] while at the same time, through the polymer's degradation, removing the nidus of inflammation at the vessel interface that is thought to be responsible for the "catch up" phenomenon of very late stent thrombosis observed with early generation drug-eluting stents (DES) [3].

The Orsiro BP-SES is available in diameters of 2.25, 2.5, 2.75, 3.0, 3.5, and 4.0 mm, and is available in lengths ranging from 9 to 40 mm. Stents with diameters of 2.25 to 3.0 mm have a strut thickness of 60 μm, while stents with diameters of 3.5 to 4.0 mm have a strut thickness of 80 μm [4]. Drawing together recent technological advances, the Orsiro coronary stent (Biotronik, Buelach, Switzerland) consists of two distinct layers packaged around its metallic struts [2].

The innermost layer of the system consists of a cobalt-chromium alloy PRO-Kinetic energy™ stent arranged in a double helix pattern, which is designed to improve flexibility and deliverability. The middle proBIO™ layer consists of a silicon carbide coating that seals the metal alloy surface and reduces the allergenic interaction of metal ions with the vessel wall and blood pool [5]. Finally, the outer BIOlute™ layer is composed of a bioabsorbable poly-L-lactic acid (PLLA) polymer containing the antiproliferative sirolimus agent. The active BIOlute™ coating is distributed in an asymmetric fashion on the struts, with a thickness of 7.5 μm on the abluminal side and a thinner 3.5-μm layer on the luminal portion of the stent. Fig. 1 demonstrates the stent strut design. The PLLA polymer undergoes a hydrolytic reaction upon contact with the blood pool, causing the polymer to break down into CO_2 and H_2O via the Krebs cycle. The sirolimus load is 1.4 μg/mm^2 [6] with the elution optimized for 12 to 14 weeks after implantation. Fig. 2 summarizes some of the key design features in comparison with other contemporary stent designs.

In vitro studies have shown that within 30 days, 50% of the drug is eluted, and within 3 months, 80% is eluted. The PLLA degrades over 2 years, leaving the thin-strut cobalt-chromium stent with minimal endothelial injury [5]. This hybrid approach of combining ultrathin struts, a passive intermediate layer, and bioabsorbable polymer is aimed at creating less flow disturbance, limiting the long-term inflammatory

Abbreviations: BP-SES, biodegradable-polymer sirolimus-eluting stent; CTO, chronic total occlusion; CI, confidence interval; DCB, drug-coated balloon; DES, drug-eluting stent; DP-DES, durable-polymer drug-eluting stent; LLL, late lumen loss; PLLA, poly-L-lactic acid polymer; PP-EES, permanent-polymer everolimus-eluting stent; STEMI, ST-elevation myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVR, target vessel revascularization.

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response at the vessel interface and encouraging rapid endothelialization with early vascular healing [1,2,5]. In larger stent diameters, where the comparative advantage of strut thickness is less (80 μm in stents with diameters >3.5 mm), the additional design features of the inert silicon carbide layer and biodegradable polymer may still confer benefits in vascular healing and long-term inflammation in comparison with other contemporary stents of similar strut thickness.

2. Discussion

Several investigator- and industry-initiated randomized controlled trials have examined the efficacy and safety of the Orsiro BP-SES in recent years. Cumulatively, these trials have enrolled close to 30,000 patients around the world and have examined de novo lesions, acute coronary syndromes, and high-risk subgroups such as small-vessel disease, diabetes, and chronic total occlusions. Table 1 describes the key randomized trials and registries, which are discussed below, followed by an additional focused discussion on the Orsiro BP-SES performance in high-risk subgroups.

2.1. The BIOFLOW trials

The introduction of drug-eluting stents (DES) brought about major advances in combating early restenosis but also raised concerns about delayed intimal healing and prolonged inflammation [7] at the site of implant, leading to late events such as stent thrombosis and in-stent restenosis [8]. The development of biodegradable-polymer stents was intended to reduce the local inflammatory response and allow improved endothelization, decreasing the risk of late events such as stent thrombosis and in-stent restenosis [9]. Starting in 2013, the BIOFLOW trials were conducted to examine the safety, efficacy, and noninferiority of the Orsiro BP-SES against several leading second-generation DES. Results of these studies were used to support regulatory approval for the use of the Orsiro stent system in Europe, Japan, China, and the United States.

BIOFLOW I [6] was a first-in-man study designed to evaluate the safety and effectiveness of the newly developed Orsiro BP-SES hybrid stent system. The trial included 30 patients with de novo lesions and demonstrated a low rate of in-stent restenosis with late lumen loss (LLL) of 0.05 ± 0.22 mm over the 9-month follow-up period. Though small, the BIOFLOW I study demonstrated that there was merit in the technology and, more importantly, that it was safe, with no myocardial infarction (MI) or stent thrombosis reported.

The follow-on BIOFLOW II [3] study was a prospective, international, randomized controlled, noninferiority trial that compared Orsiro BP-SES in a 2:1 allocation ratio with the benchmark stent of the day, Xience Prime (Abbott Vascular, Santa Clara, California). The trial also included a subgroup analysis, which allocated patients to repeat optical coherence tomography (OCT) for disease occurring in small vessels (<2.75 mm diameter) and diabetic patients ($n = 55$). The initial 9-month follow-up data published in 2015 showed non-inferior LLL compared with Xience (Orsiro 0.10 ± 0.32 mm vs. Xience 0.11 ± 0.29 mm, $p_{noninferiority} < 0.0001$). Similar to BIOFLOW I, no events of definite or probable stent thrombosis were reported in the Orsiro BP-SES group (298 patients, 332 lesions) [3]. The 5-year clinical follow-up data released in 2018 showed noninferior target lesion failure (TLF) (Orsiro 10.4% vs. Xience 12.7%, $p = 0.473$) with significantly lower mortality in vessels <2.75 mm (Orsiro 3.7% vs. 11.3%, $P = 0.022$), [10] suggesting that the 60-μm thin Orsiro BP-SES profile may provide additional benefit in small-vessel subgroups. The recent publication of BIOFLOW VI [11] in China confirms the noninferior rates of LLL (Orsiro 0.05 mm ± 0.21 mm vs. Xience Prime 0.07 mm ± 0.2 mm) and TLF (Orsiro 2.3% vs. Xience 1.8%, $p = 0.7505$) when compared with Xience.

The BIOFLOW III [12,13] trial built on the findings of BIOFLOW II and aimed to gather "real world" data on TLF at 12 months using a prospective, open-label, registry-based design. Enrolling close to 1400 patients, the registry reported a TLF rate of 5.1% over 12 months (95% CI 4.0% to 6.4%), with a rate of 10% (95% CI 8.4% to 12.0%) in the 5-year follow-up study [12]. Low rates of stent thrombosis similar to previous trials were observed (0.2% at 12 months, 95% CI 0.1% to 0.7%).

BIOFLOW IV [14] was designed as a noninferiority trial to allow regulatory approval in Japan. A total of 579 patients with de novo lesions were randomized in a 2:1 fashion to receive Orsiro BP-SES vs. the Xience permanent-polymer everolimus-eluting stent (PP-EES). Patients for planned intervention and patients presenting with MI in the previous 72 h were excluded. A total number of 385 patients (441 lesions) were enrolled. Twelve-month follow-up data reported a noninferior rate of target vessel failure (TVF) in de novo lesions compared with Xience (Orsiro 5.5% vs. Xience7.5%, $p_{noninferiority} < 0.0001$). These data echoed the previous European BIOFLOW I, II, and III findings with similar rates of TLF and stent thrombosis, demonstrating applicability of those findings to the Japanese population and facilitating Japanese regulatory approval in January 2018 [15]. Five-year follow-up is ongoing, with results expected in 2024.

With regulatory approval in hand in both Europe and Japan, the BIOFLOW V [2] trial randomized patients to receive Orsiro BP-SES or Xience in patients presenting for elective or urgent percutaneous coronary intervention (PCI) at 90 hospitals across 13 countries, including the United States for the first time. The primary endpoint of the trial was TLF at 12 months. Of patients included in the study, 51% presented with an acute coronary syndrome. Although BIOFLOW V was powered as a noninferiority trial, over the initial 12-month period, the incidence of TLF was significantly lower in the Orsiro BP-SES group than in the Xience DP-EES group (Orsiro 6.2% vs. Xience 9.6%, $p = 0.0399$) and was likely driven by a lower rate of target vessel MI in the Orsiro BP-SES group (Orsiro 5% vs. Xience 8%, $p = 0.0155$) [16].

In order to improve endpoint detection and statistical significance, the authors of BIOFLOW V incorporated the results of BIOFLOW II and IV and used a Bayesian analysis [17]. This pooled analysis showed a TLF rate of 3% in the Orsiro BP-SES group with a posterior probability for noninferiority of 100% and a posterior probability of superiority of 97% [2]. A subsequent landmark analysis of the BIOFLOW V data confirmed that the statistically significant differences in TLF and target vessel MI reported at one year persisted through two-year follow-up [18]. Shortly after BIOFLOW V's publication, the Food and Drug Administration granted approval for use of the device in the United States [19].

2.2. The BIOSCIENCE, BIO-RESORT, BIONYX, and SORT OUT VII and IX trials

In addition to the data provided by the BIOFLOW studies, several large-scale investigator-initiated trials demonstrating the safety and efficacy of the Orsiro BP-SES have also emerged. Fig. 3 shows rates of TLF at 12 months from selected prospective randomized controlled trials comparing the Orsiro BP-SES with the Xience PP-EES.

The BIOSCIENCE [1] trial, published in 2014, was similar to BIOFLOW II in design and was a large scale, 1:1 randomized noninferiority trial. Unlike BIOFLOW II, however, patients with acute coronary syndrome in the preceding 72 h were included. Patient enrollment was completed in 12 months, with 2119 patients and 3139 lesions enrolled. The primary endpoint of TLF at 12 months showed that Orsiro BP-SES was non-inferior to Xience DP-EES (Orsiro 6.5% vs. Xience 6.6%, $p_{noninferiority} < 0.0004$), similar to the findings of BIOFLOW II. A novel finding, however, was the subgroup analysis in patients treated with ST-elevation myocardial infarction (STEMI). In the prespecified subgroup of acute coronary syndromes with STEMI, the Orsiro BP-SES was associated with a lower risk of TLF than the Xience PP-EES at 12 months (Orsiro 3.3% vs. Xience 8.7%, $p = 0.024$) [1,20]. The BIOSCIENCE 5-year follow-up data [20] failed to show any difference in the TLF rate at 5 years between the two groups, suggesting that the reduction seen at 12 months may be related to the BP-SES's ultrathin struts, and that after complete

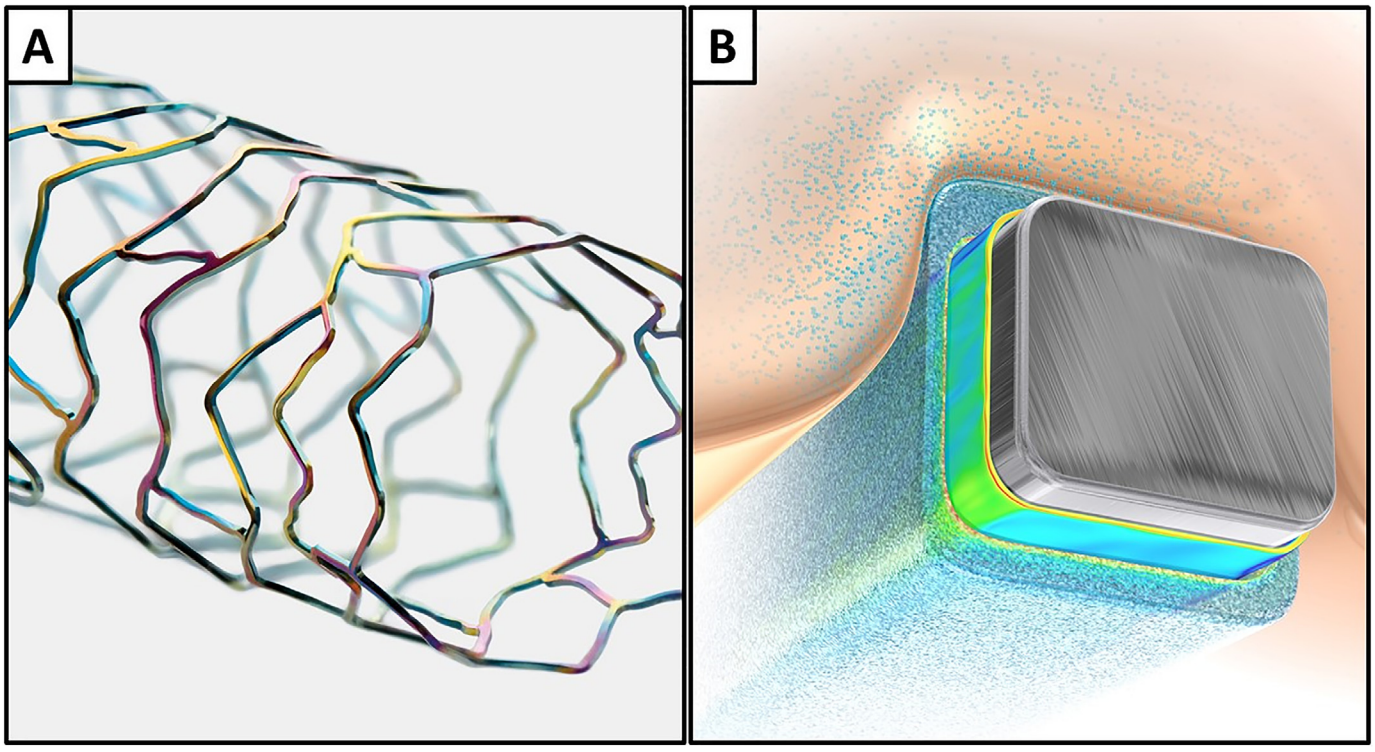

Fig. 1. A) The open-cell double-helix of the ultrathin-strut Orsiro biodegradable-polymer sirolimus-eluting stent is designed for flexibility and deliverability. B) Cross-section of the ultrathin biodegradable-polymer strut showing the innermost cobalt chromium alloy PRO-Kinetic energy™ stent, the middle proBIO™ silicon carbide layer that seals the metal alloy surface and reduces the allergenic interaction of metal ions with the vessel wall and the outer BIOlute™ layer is composed of a bioabsorbable poly-L-lactic acid (PLLA) polymer containing the antiproliferative sirolimus agent. Images provided by and used with the permission of Biotronik (BIOTRONIK, Buelach, Switzerland).

breakdown of the biodegradable polymer, the risk of very late TLF is similar to that observed with permanent-polymer stents.

One question that remained after the publication of the early BIOFLOW trials and the BIOSCIENCE trial was whether the low rates of TLF observed with the Orsiro BP-SES were due to the thin strut design and the absence of a permanent-polymer stent within the vessel wall, reducing vascular inflammation and the development of neoatherosclerosis. The BIO-RESORT [21] study aimed to answer this question using a large-scale, multicenter three-arm randomized control trial. The 3514 patients who were enrolled included all-comers and acute coronary syndromes with minimal exclusion factors and randomized patients to receive one of three stents. The very-thin-strut Orsiro BP-SES (60 μm), the very-thin-strut Synergy biodegradable-polymer everolimus-eluting stent (74 μm, BP-EES) or the thin-strut Resolute

	Abbott/Boston Xience/Promus	Medtronic Resolute Onyx	Biosensors BioMatrix	Terumo Nobori	Terumo Ultimaster	Boston Synergy	Biotronik Orsiro
STENT PLATFORM							
	CoCr/PtCr	CoNi	316L SS	316L SS	CoCr	PtCr	CoCr
STRUT THICKNESS							
	81 μm	81 μm	120 μm	120 μm	80 μm	74 μm	60 μm
POLYMER COATING							
	DURABLE POLYMER		BIOABSORBABLE POLYMER				
	PVDF-HFP	BioLinx	PLA	PLA	PDLLA-PCL copolymer	PLGA	PLLA
POLYMER DEGRADATION							
	n/a	n/a	6-9 mo	6-9 mo	3-4 mo	4 mo	> 12 mo
POLYMER DISTRIBUTION							
	Circumferential	Circumferential	Abluminal	Abluminal	Abluminal	Abluminal	Circumferential
	7-8 μm/side	6 μm/side	10 μm	20 μm	15 μm	4 μm	4-7 μm/side
DRUG TYPE/DOSAGE							
	Everolimus	Zotarolimus	Biolimus A9	Biolimus A9	Sirolimus	Everolimus	Sirolimus
	1.0 μg/mm²	1.6 μg/mm²	15.6 μg/mm	15.6 μg/mm	3.9 μg/mm	113 μg / 20 mm	1.4 μg/mm²

Adapted from Iglesias et al., Orsiro cobalt-chromium sirolimus-duting stent: present and future perspectives, DOI: 10.1080/17434440.2017.1378091

Fig. 2. Figure displaying the comparative strut thicknesses, polymer coatings, polymer degradation periods, distribution of the polymer, the eluted drug and drug load. Images provided by and used with the permission of Biotronik (BIOTRONIK, Buelach, Switzerland), from: Iglesias et al., Orsiro cobalt-chromium sirolimus-eluting stent: present and future perspectives, DOI: https://doi.org/10.1080/17434440.2017.1378091

Table 1
Summary table of studies describing study design highlights, number of patients enrolled, number of lesions treated, primary endpoints, and key findings of large scale, prospective randomized controlled trials and registries for the Orsiro bioresorbable-polymer sirolimus-eluting stent (BP-SES). LLL = Late lumen loss, TLF = Target lesion failure (composite of cardiovascular death, target vessel-related myocardial infarction, or ischemia-driven target lesion revascularization), TVR = Target vessel failure (composite of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization), MACE = major adverse cardiovascular events, TLR = target vessel revascularization, MI = myocardial infarction, OCT = optical coherence tomography.

Study name	Study design highlights	Total patients	Patients in BP-SES arm	Lesions in BP-SES arm	Primary endpoint	Key findings
BIOFLOW I	- First in man - Multi-center - Single arm registry - Single de novo lesions	30	30	30	LLL at 9 months	- LLL 0.05 ± 0.22 mm at 9 months. - 10% MACE (1 cardiac death, 2 non-cardiac deaths). - 2 patients with TLR. - No MI or stent thrombosis.
BIOFLOW II - 12 month	- Orsiro vs. Xience Prime - ≤2 De-novo lesions	452	298	332	LLL at 9 months	- Non-inferior LLL at 9 months - Orsiro 0.10 ± 0.32 mm vs. Xience 0.11 ± 0.29 mm (p-value for non-inferiority <0.0001). - Clinical endpoints comparable to Xience over 12-month follow up.
BIOFLOW II - 5 year					TLF at 60 months	- Non-inferior TLF at 5 years - Orsiro 10.4% vs. Xience 12.7% (p = 0.473). - No stent thrombosis in Orsiro group. - Numerically more TLR in diabetes treated with Orsiro, but not statistically significant (13.5% vs. 4.5%, p = 0.138). - Orsiro showed significantly lower 5-year mortality in small vessel disease (<2.75 mm) - (3.7% vs. 11.3%, p = 0.022).
BIOFLOW III	- Single arm registry - All-comers	1356	1356	1738	TLF at 12 months	- TLF rate of 5.1% at 12 months (95% CI 4.0–6.4%). - Cardiac death 1.3% (95% CI 0.9–2.1%). - Definite stent thrombosis 0.2% (95%CI 0.1–0.7%).
BIOFLOW III - 5 year					TLF at 60 months	- TLF rate of 10% at 5 years (95% CI 8.4–12%). - TLF, cardiac death and MI rates higher in diabetes compared with non-diabetes, but TLF still low at 14%
BIOFLOW IV	- Orsiro vs. Xience Prime (2:1) - ≤ 2 De-novo lesions - ACS excluded	575	385	441	TVF at 12 months	- Non-inferior TVF at 12 months - Orsiro 5.5% vs. Xience 7.5% (p-value for non-inferiority <0.0001). - 5-year follow up is ongoing.
BIOFLOW V	- Orsiro vs. Xience (2:1) - STEMI, bypass grafts, ISR, CTO's excluded	1334	884	–	TLF at 12 months	- Superior rate of TLF compared to Xience* - Orsiro 6.2% vs. 9.6% in Xience group at 12 months (p = 0·0399). - Lower cardiac death or MI in Orsiro group at 24 months (5% vs. 9%, p = 0.072).
BIOFLOW VI	- Orsiro vs. Xience Prime (1:1) - ACS, grafts, CTO's, bifurcation & calcified lesions excluded	440	223	257	LLL at 9 months	- Non-inferior LLL at 9 months - Orsiro 0.05 mm ±0.21 mm vs. Xience Prime 0.07 mm ±0.2 mm (p-value non-inferiority <0.0001). - TLF similar – Orsiro 2.3% vs. Xience 1.8% (p = 0.7505) - Final publication pending
BIOLUX RCT	- Pantera Lux drug coated balloon (DCB) with Orsiro in ISR (2:1)	229	72	80	LLL at 6 months	- Non-inferior to DCB in ISR - LLL in Orsiro 0.2 mm vs. 0.03 mm in DCB group (p = 0.39).
BIOSCIENCE	- Orsiro to Xience Prime (1:1) - All-comers	2119	1063	1594	TLF at 12 months	- Non-inferior TLF at 12 months - Orsiro 6.5% vs. Xience 6.6% (p-value for non-inferiority <0.0004)
BIOSCIENCE - 5 year					TLF at 60 months	- Non-inferior TLF at 5 years - Orsiro 20.2% vs. Xience 18.8%. In subgroup analysis Orsiro demonstrated lower TLF in STEMI patients at 5 years compared to Xience (RR 0.38, 0.16–0.91)
BIO-RESORT	- Orsiro, Synergy or Resolute Integrity (1:1:1) - All-comers	3514	1169	1551	TVF at 12 months	- Non-inferior TVF at 12 months - (Orsiro 4.7% vs. Resolute Integrity 5.4%, p non-inferiority <0.0001) - Orsiro had numerically lowest rates of TVF, TLF, TLR, cardiac death, stent thrombosis and MACE - Landmark analysis suggests Orsiro may reduce risk of TLR at 1 year
SORT OUT VII	- Orsiro vs. Nobori (1:1) - All-Comers	2525	1261	1590	TLF at 12 months	- Non-inferior TLF at 12 months - Orsiro 3.8 vs. Nobori 4.6% (0.12–0.92; P = 0.034). - Orsiro demonstrated reduced risk of definite stent thrombosis at 12 months (0.4% vs. 1.2%, p = 0.03).
BIONYX	- Orsiro vs. Resolute Onyx (1:1) - All-comers	2488	1245	1593	TVF at 12 months	- Non-inferior TVF at 12 months - Orsiro 4.5% vs. Resolute Onyx 4.7% (p-value for non-inferiority <0.0005). - Definite or probable stent thrombosis low in both groups - Orsiro 0.7% vs. Resolute Onyx 0.1%.
SORT OUT IX	- Orsiro vs. BioFreedom (1:1) - All-comers	3150	1579		TLF at 60 months	- BioFreedom did not meet criteria for non-inferior TLF compared with Orsiro (Orsiro 4.0% vs. BioFreedom 5.3%, p-value non-inferiority <0.123). - Orsiro had significantly less TLR at 12 months (Orsiro 1.3% vs. BioFreedom 3.5%, p ≤0.0001).
SORT OUT X	- Orsiro vs. CD4 Combo stent (1:1)	3148	c.1570	–	TLF at 12 months	- Ongoing
BIOSTEMI	- Superiority trial - Orsiro vs. Xience	1300	649	–	TLF[ψ] at 12 months	- Superior rates of TLF at 12 months – Orsiro 4% vs. Xience 6% (rate ratio 0.59, posterior probability of superiority 0.986)

(continued on next page)

Table 1 (*continued*)

Study name	Study design highlights	Total patients	Patients in BP-SES arm	Lesions in BP-SES arm	Primary endpoint	Key findings
	(1:1) - STEMI patients					
ORIENT	- Orsiro vs. Resolute Integrity (2:1) - All-comers	372	250	345	LLL at 9 months	- Non-inferior LLL at 9 months - (Orsiro 0.10 ± 0.35 mm, Resolute Integrity 0.16 ± 0.39 mm, p for non-inferiority <0.001)
HATTRICK-OCT	- Orsiro vs. Endeavour Resolute (1:1) - ACS patients with de novo lesions in LAD	44	23	23	Strut coverage by OCT, vasodilator response at 3 months	- Proportion of uncovered struts by OCT less in Orsiro (Orsiro 3.9% vs. Endeavour Resolute 8.9%) at 3 months.
PRISON IV	- Orsiro vs. Xience - CTO's (1:1)	330	165	165	LLL at 9 months	- Orsiro failed to meet criteria for non-inferior LLL at 9 months in recanalized CTO's (Orsiro 0.13 ± 0.63 mm vs. Xience 0.02 ± 0.47 mm, p non-inferiority = 0.11), sub group analysis suggested difference most pronounced in Orsiro stents <3.0 mm.
		23,406	10,652	9739		

Integrity durable-polymer zotarolimus-eluting stent (91 μm, DP-ZES). Over 12 months, the Orsiro BP-SES proved to be noninferior to the durable-polymer Resolute Integrity stents and had similar rates of TVF as the Synergy BP-EES [21,22].

Follow-up data at 2 years showed that TVF was not statistically different between the three stents; however, when TLF was examined using a landmark analysis between 12 and 24 months, Orsiro BP-SES fared better than Resolute, with a target vessel revascularization (TVR) rate of 0.6% for Orsiro compared with 1.5% for Resolute, suggesting that Orsiro BP-SES reduced the risk of revascularization after 1 year of follow-up [22].

Based on the rates of TLF seen in the BIOFLOW V [2] and BIO-RESORT [21,22] studies, the Orsiro BP-SES was selected as the comparator for the first randomized controlled trial of the newly designed Resolute Onyx stent (Medtronic, Santa Rosa, California, USA) in the BIONYX trial [23]. Resolute Onyx was developed as a thin-strut durable-polymer zotarolimus-eluting stent system. The trial included all comers, randomizing 2516 patients in a 1:1 fashion. Both stents showed excellent safety and efficacy, with low rates of definite or probable stent thrombosis in both groups (Orsiro 0.7% vs. Onyx 0.1%, hazard ratio 0.11 [95% CI 0.01–0.87]; $p = 0.0112$). The primary endpoint of TLF at 12 months was similar in both the Orsiro BP-SES and Onyx groups [23]. Funding has been secured for up to three years of follow-up, with two-year data expected in the coming months.

Whereas the BIOFLOW, BIO-RESORT, BIOSCIENCE, and BIONYX trials compared Orsiro BP-SES to durable-polymer systems, the SORT OUT VII trial [24] was the first head-to-head trial against a biodegradable-polymer system. The registry-based, multicenter, noninferiority trial randomized patients to receive the Orsiro BP-SES or the Nobori (stainless-steel, biolimus-eluting, 120-μm strut) stent. The trial enrolled 2525 patients, with TLF at 12 months being the primary endpoint. Orsiro BP-SES was shown to be noninferior to Nobori at 12 months with respect to TLF (Orsiro 3.8% vs. Nobori 4.6%, 95% CI 0.12–0.92; $p_{noninferiority} = 0.034$). The rates of reported TLF were most likely lower than reported in the large BIOSCIENCE trial (6.5%), as the SORT OUT (3.8%) trial excluded procedure-related MI because of the registry-based design. In addition, the Orsiro BP-SES demonstrated a statistically lower rate of definite of probable stent thrombosis at 12 months (Orsiro 0.4% vs. Nobori 1.2%, $p = 0.03$) [24].

Further studies against polymer-free drug-coated stents, such as the SORT OUT IX [25] trial, showed that the biolimus-based BioFreedom stent failed to meet the criteria for noninferiority of TLF at 12 months compared with Orsiro BP-SES, likely driven by a lower rate of target lesion revascularization (TLR) in the Orsiro BP-SES arm of the study [26]. Recent meta-analyses have suggested that the improved rates of TLF may be related to an increased risk of stent thrombosis in thick-strut platforms such as 120-μm Nobori and 120-μm BioFreedom stents compared with the 60-μm Orsiro BP-SES system [27–29].

Data provided by the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) corroborate the results seen in randomized trials. An analysis over the 6-year period from October 2011 to June 2017 including 74,131 patients (4561 in the Orsiro group compared to 69,570 who received other frequently used DES) showed significantly lower rates of TLR in the Orsiro group (Orsiro 1.6% vs. other DES 2.3%, adjusted HR 0.75, 95% CI 0.60–0.94; $p = 0.012$) [30].

2.3. Evidence in high-risk subgroups

PCI in high-risk subgroups can present several challenging patient and lesion characteristics and can result in increased rates of in-stent restenosis, TVF, and stent thrombosis. The following section will address the performance of the Orsiro BP-SES in these high-risk subgroups.

2.3.1. ST-elevation myocardial infarction

Patients presenting with STEMI pose several challenges to PCI. Malapposition of stent struts may result from undersizing and subsequent thrombus resolution, setting the stage for an increased risk of early stent thrombosis [31]. Although the development of DES allowed for substantial improvements in early stent thrombosis, concerns remained about delayed vascular healing due to hypersensitivity and inflammation induced by permanent-polymer stents [32,33]. The thin-strut profile coupled with the inert silicon carbide coating of the Orsiro BP-SES has shown promise in reducing rates of TLF, based on subgroup analyses in larger recent trials [2,20,31,34].

The BIOSCIENCE trial's 12- and 24-month [1,22] results demonstrated improved outcomes in STEMI patients. Twelve-month rates of TLF were reported at 3.3% vs. 8.7% in the BP-SES and DP-EES groups (risk ratio [RR] 0.38, $p = 0.024$) with 24-month data showing rates of 5.4% vs 10.8% (RR 0.48, $p = 0.043$) [32]. Most notably, the lower observed rates of TLF appeared to be driven by decreased rates of cardiac death or MI in the BP-SES group (RR 0.46, 95% CI 0.21–1.02, $p = 0.05$) [32]. BIOFLOW V data showed a similar reduction in TLF with a reported hazard ratio of 0.50 (95% CI 0.28–0.89) compared to DP-EES [2].

The combined results of the BIOFLOW V and BIOSCIENCE noninferiority trials and the demonstrated improved outcomes led to the design of the BIOSTEMI trial [35]. The trial enrolled 1300 patients presenting with STEMI with 1:1 randomization to the BP-SES or DP-EES treatment group. Unlike previous trials powered for noninferiority, BIOSTEMI demonstrated, for the first time, clear superiority with respect to rates of TLF at 12 months in patients presenting with STEMI (Orsiro 4% vs. Xience 6%, rate ratio 0.59, posterior probability of superiority 0.986) [36]. The difference in the rates of TLF was driven primarily by fewer cases of clinically indicated TLR in the Orsiro group.

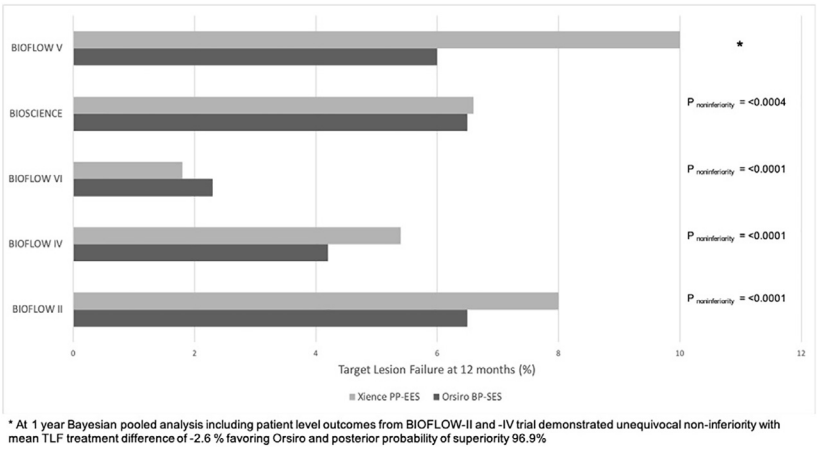

Fig. 3. Rates of target lesion failure at 12 months from selected prospective randomized controlled trials comparing the Orsiro biodegradable-polymer sirolimus eluting stent (BP-SES) to the Xience permanent-polymer everolimus-eluting stent (PP-EES).

2.3.2. Chronic total occlusions

Chronic total occlusions (CTOs) present one of the toughest environments for stent performance with respect to in-stent thrombosis and late or very late in-stent restenosis [37,38]. When compared to de novo lesions, CTOs are typically longer and more calcified, often require multiple stents with overlapping segments, and may undergo late vessel remodeling as blood flow increases, leading to vasodilation and stent-strut malapposition, setting the stage for thrombosis or in-stent restenosis [39,40]. The PRISON IV [40] trial set out to evaluate the Orsiro BP-SES performance in this challenging population. Enrolling 330 patients, the trial randomized patients to receive Orsiro BP-SES or Xience in a 1:1 allocation. Of patients enrolled in both arms of the trial, 99% underwent repeat angiography at 9 months and clinical follow-up at 12 months. PRISON IV failed to meet the primary endpoint of noninferior LLL at 9 months of Orsiro BP-SES compared with Xience and showed a significantly higher rate of binary restenosis in the Orsiro BP-SES group (Orsiro 8.0% vs. Xience 2.1%, $p = 0.028$).

The recent publication of the 3-year follow up data of the PRISION IV trial [41] gives the best long-term follow up of the Orsiro BP-SES's performance in CTOs. Over the three years of follow-up, the cumulative incidence of major adverse clinical events was higher in the Orsiro BP-SES arm than in the Xience EES arm (9.7% vs. 4.2%). Similar trends were also seen with respect to TLR over the study period favoring Xience with TLR rates reported as 9.7% in the Orsiro arm versus 3.4% in the Xience arm. A landmark analysis demonstrated that after one year, rates of TLR overall remained low but were higher in the Orsiro arm than in the Xience arm (2.1% vs. 0.6%, *p*-value reported as "NS") [41].

In a smaller, non-randomized study, Markovic et al. [38] examined LLL at 9 months in patients receiving the Resolute Integrity zotarolimus-eluting stent versus the Orsiro BP-SES. Rates of LLL were significantly less in the Orsiro BP-SES arm (Orsiro 0.24 ± 0.53 mm vs. Resolute Integrity 0.59 ± 0.72 mm, $p = 0.01$), but this did not translate into a difference in clinical events up to 24 months of follow-up.

Although PRISON IV failed to show noninferiority with respect to LLL, the study was underpowered to detect clinical endpoints. The rates of TVR were higher in PRISON IV compared with BIOSCIENCE (9.2% vs. 4%), but this was probably due to the routine angiographic follow-up at 9 months in the PRISON IV trial as opposed to reported clinical events in the BIOSCIENCE trial. Subgroup analyses have demonstrated that the majority of the LLL seen within the PRISON IV study is due to stents with <3 mm in diameter (60-μm strut thickness) vs. stents >3 mm in diameter (80-μm strut thickness) [42]. An additional OCT subgroup analysis demonstrated favorable strut coverage in the Orsiro arm [43]. Despite these findings, results from CTO patients in BIOFLOW III [12,13] and SORT OUT VII [44] suggest that rates of TLF and TLR remain low in CTO subgroups.

2.3.3. Diabetes

A recent meta-analysis pooling diabetic patients from the BIOFLOW II, IV, and V trials examined TLF at 1 year. The analysis included 494 diabetic patients treated with Orsiro BP-SES and 263 patients treated with Xience across the three BIOFLOW trials. Rates of TLF were similar at one year: 6.3% in the Orsiro BP-SES group and 8.7% in the Xience group (HR 0.82, 95% CI 0.047–1.43, $p = 0.493$) [16]. These findings were confirmed in a subgroup analysis of the SORT OUT VII trial [45]. Rates of TLF among patients treated with or without insulin were also found to be similar [45].

2.3.4. Small-vessel disease

Small-vessel disease, generally defined as vessels <2.75 mm in diameter, has been associated with a greater risk of TLR due to increased rates of in-stent restenosis [46,47]. Data from BIOFLOW II [10] and a subgroup analysis from BIO-RESORT [48] suggest that the ultrathin Orsiro BP-SES may provide additional benefit in small-vessel subgroups.

BIOFLOW II contained 259 patients within the small-vessel subgroup (≤2.75 mm) and demonstrated 5-year TLF rates of 11.1% in the BP-SES arm vs. 15.5% in the DP-EES arm ($p = 0.303$), a difference that was mainly due to a lower rate of death in the BP-SES arm (3.7% vs. 11.3%, $p = 0.039$) [10]. A subsequent analysis of the BIO-RESORT trial examined the 3-year outcomes in 1506 of the 3514 total trial participants. A multivariate analysis later showed that BP-SES was independently associated with lower rates of TLR at 3 years in comparison with the everolimus and zotarolimus treatment groups (adjusted HR 0.42, 95% CI 0.20–0.85, $p = 0.02$). No differences were reported in the rates of cardiac death, target vessel MI, or stent thrombosis at 3 years [48].

Results from the small-vessel cohort of the BIOSCIENCE trial [47] released in August 2019 differed somewhat from the results of the BIOFLOW II and BIO-RESORT small-vessel subgroups. The ≤2.75-mm small-vessel cutoff used in BIOFLOW II and BIO-RESORT, versus the definition of ≤3 mm or > 3 mm to define small- versus large-vessel disease used in BIOSCIENCE, potentially accounts for the discrepant results. Five-year rates of TLF were not found to be significantly different between the BP-SES and DP-EES groups (22.3% vs. 18.3%, respectively; rate ratio 1.22, 95% CI 0.94–1.58, $p = 0.13$) [47].

2.3.5. In-stent restenosis

Despite recent advances in stent technology, neoatherosclerosis due to inflammation, drug toxicity, and delayed vascular healing can result in revascularization rates of up to 10% [4,49]. The inert silicon carbide proBIO layer has the potential to improve biocompatibility at the vessel interface and to reduce the proliferation of tissue, which leads to in-stent restenosis. However, to date, there are limited available randomized data on the efficacy of BP-SES versus existing second-generation DES in treating in-stent restenosis, with only 10 patients within the all-comer BIOSCIENCE trial and 30 within BIO-RESORT.

Current European guidelines advocate for the use of drug-coated balloons (DCBs) or DES in the treatment of in-stent restenosis, but there are limited data on the efficacy of latest-generation stents [50]. The BIOLUX trial [49] aimed to address this gap, randomizing 229 patients with in-stent restenosis in a 2:1 fashion to receive treatment with a butyryl trihexyl citrate (BTHC)-based paclitaxel DCB versus BP-SES. In-stent LLL at 6 months and TLF at 12 months were compared between both groups. Over the study period, DCB proved noninferior to BP-SES, with LLL in DCB arm reported at 0.03 ± 0.40 mm and 0.20 ± 0.70 mm in the BP-SES arm ($p = 0.40$). Rates of TLF at 12 and 18 months were also similar, demonstrating that both options seem feasible and effective but that further studies are needed in this challenging cohort of patients [49].

2.4. Economic impact

In addition to the improved clinical outcomes demonstrated in the BIOFLOW V trial, recent economic modeling has also suggested possible economic benefits [51]. Markov economic modeling has shown that the reduction in rates of TLR and target vessel MI resulted in a cumulative reduction of $2415 per patient over a 48-month period compared to Xience [52]. With rising healthcare costs, these savings are an important consideration, not only for individual patients and insurance payers, but also for healthcare policymakers [51]. While caution should be exercised in interpreting this single sub-analysis, healthcare spending in the US alone is projected to reach 20% of gross domestic product by 2025 [53], so the delivery of safe, clinically effective and potentially economically viable treatments is an important consideration for any healthcare system.

3. Limitations

The Orsiro BP-SES does have some notable limitations. The presence of the ultrathin struts may make the stent a less favorable choice in situations requiring high radial force to prevent vessels recoil, such as CTOs, as described in a previous section. Additionally, data on the performance of the Orsiro BP-SES in heavily calcified lesions is limited, mainly arising from small subgroups of “all-comers” trials, making any definite statements about the device's performance in this space difficult.

On a practical level, the ultrathin-stent struts can be difficult to visualize using fluoroscopy, so careful confirmation of the stent position should be performed before deployment.

4. Future directions

Several ongoing trials are continuing to investigate the efficacy and effectiveness of the Orsiro BP-SES in comparison to other contemporary stents. The enhanced biocompatibility and ultrathin-strut design may also have a role to play in high-bleeding-risk populations by allowing for shortened dual antiplatelet therapy duration, which will be examined in the planned BIOFLOW-DAPT study. With the favorable outcomes of the Orsiro BP-SES, ongoing developments in stent technology, such as the incorporation of CD34+ antibodies into bioabsorbable-polymer stents (COMBO™, OrbusNeich, Hoevalaken, the Netherlands), aimed at encouraging endothelial progenitor cell growth and vascular healing, are now being compared to the Orsiro BP-SES [54].

5. Conclusions

Overall, the Orsiro BP-SES has demonstrated its safety and noninferiority in numerous randomized clinical trials [1,3,14,20,48]. The combination of the ultrathin-strut design and inert proBIO silicon carbide layer allowing enhanced biocompatibility has demonstrated low rates of TLR against comparators and low rates of stent thrombosis. In specific high-risk subgroups, such as patients with STEMI and CTOs, notable exceptions have emerged, with lower rates of cardiac death and MI in STEMI patients [36], yet higher rates of TLR and major adverse cardiac events suggested in patients with CTOs [41]. Additional appropriately powered randomized controlled studies are needed to examine the role of the Orsiro BP-SES in other high-risk subgroups, including high-bleeding-risk patients, CTOs, and in-stent restenosis.

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