

The Impact of Thin-Strut, Biodegradable Polymer Stent Designs

How these stent design characteristics may affect PCI outcomes going forward.

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New-generation drug-eluting stents (DESs) currently represent the standard of care among patients undergoing percutaneous coronary intervention (PCI). Compared with earlier-generation devices, newer-generation DESs typically feature the following key aspects: a lower drug load with predominant use of limus agents, thinner stent struts, biodegradable polymers or permanent polymers with a more biocompatible profile, and the preferential use of cobalt chromium or platinum chromium platforms.¹

Strut thickness in early-generation DESs was 140 μm for the Cypher sirolimus-eluting stent (SES; Cordis Corporation) and 132 μm for the Taxus paclitaxel-eluting stent (PES; Boston Scientific Corporation), whereas, with few exceptions, strut thickness in new-generation DESs is < 100 μm , with most recent platforms engineered with ultrathin struts reaching approximately 60 μm . Therefore, despite the lack of a consensus definition, a threshold of 100 μm seems appropriate to define thin-strut (< 100 μm) versus thick-strut ($\geq$ 100 μm) coronary stents.

WHY STRUT THICKNESS IS IMPORTANT

Since the era of bare-metal stents, preclinical evidence exists surrounding the role of stent strut geometry and thickness on parameters of safety and efficacy. In a model of ex vivo flow loops, Kolandaivelu and colleagues showed that thick-strut stents (162 μm) were 1.5-fold more thrombogenic than otherwise identical stents with thinner stent struts (81 μm).² Moreover, in the same study, thick-strut stents implanted in porcine coronary arteries presented more thrombus and fibrin deposition than thin-strut stents at 3 days after implantation, with approximately 60% more thrombus formation.² Along this line, in a preclinical study of a rabbit denudation

model, strut tissue coverage at 14 days was highest (95%) in stents with the thinnest struts (81 μm) compared with thicker platforms (88% and 77% with 97- and 132- μm platforms, respectively).³ As a likely mechanism, strut thickness is thought to modulate local blood flow, with stagnation and recirculation more likely to occur in correspondence with thick instead of thin struts. Furthermore, stent endothelialization is expected to be faster with thin-strut stents than thick-strut stents due to a smaller area requiring neointimal tissue coverage.

There is also evidence that strut thickness plays a role in the efficacy profile of coronary devices. In the ISAR-STEREO trial, the use of thin-strut (50 μm) instead of thick-strut (140 μm) bare-metal stents resulted in a significant reduction of binary restenosis at 6-month angiographic follow-up (15% vs 25.8%; $P = .003$), leading to a clinical benefit in terms of the need for repeat intervention at the target vessel (8.6% vs 13.8%; $P = .03$).⁴ As a possible explanation, a thick strut induces more local coronary inflammation, greater vessel injury, and disruption of the internal elastic lamina due to a more traumatic effect compared to thin-strut stents. Thus, the greater intimal inflammation associated with the deployment of thick struts promotes in-stent neointimal growth and hyperplasia, eventually leading to restenosis.⁵

Finally, other potential advantages of coronary stents equipped with thinner struts include increased flexibility, reduced stent profile, improved trackability, and a lower risk of side branch occlusion.

CLINICAL DATA ON BIODEGRADABLE POLYMER DESs

The transition from stainless steel to cobalt chromium and, more recently, to platinum chromium

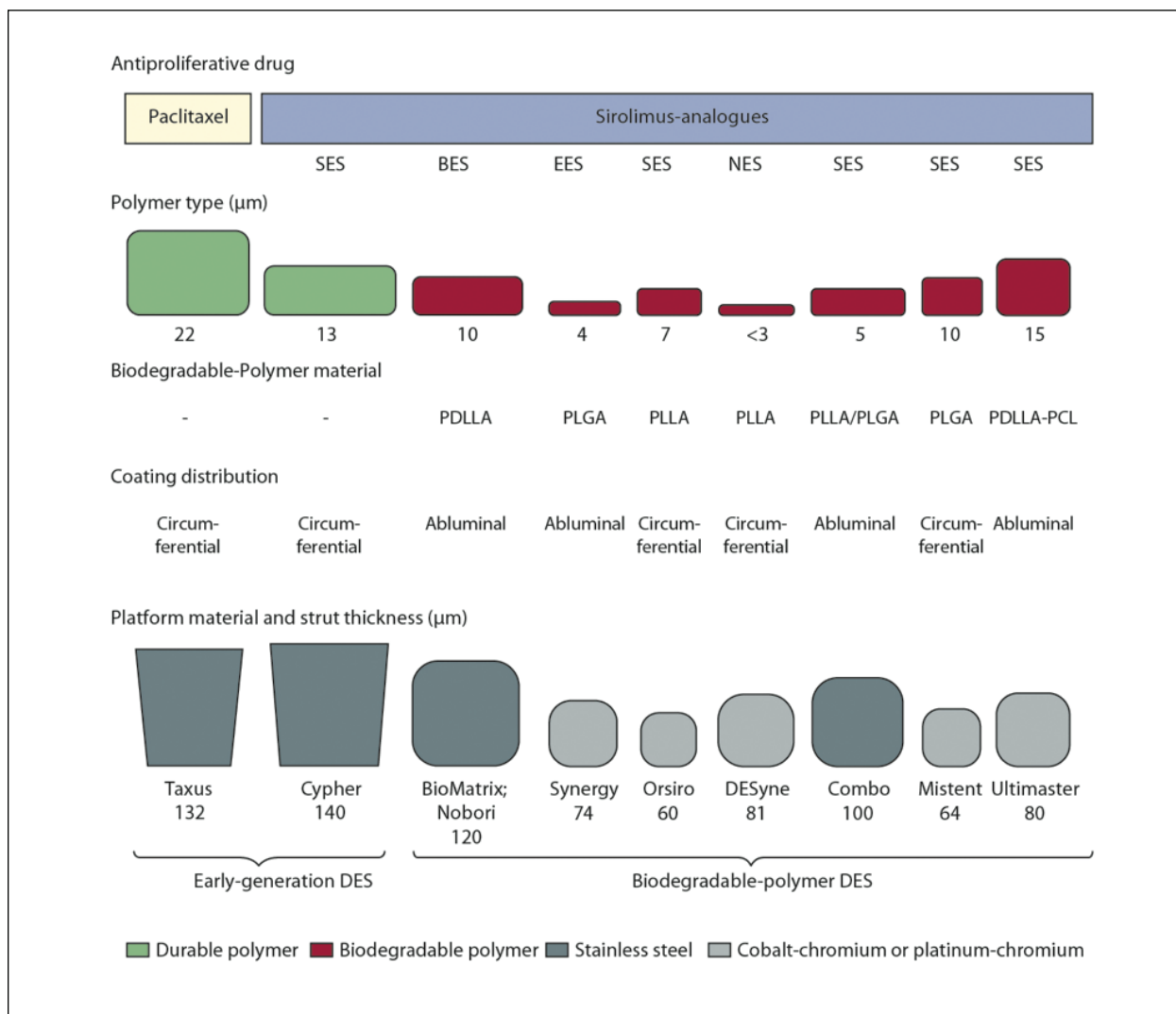


Figure 1. Comparison of early-generation versus new-generation biodegradable polymer DESs. NES, novolimus-eluting stent; PDLLA, poly(DL-lactic acid). Adapted from Piccolo R, Giustino G, Mehran R, Windecker S. Stable coronary artery disease: revascularisation and invasive strategies. *The Lancet*. 2015;386:702–713, with permission from Elsevier.

platforms has been key in decreasing strut thickness in new-generation DESs as it allowed for a 40% to 60% reduction in strut thickness without affecting radial strength. However, when clinical data on new-generation DESs are analyzed, it is nearly impossible to disentangle the sole effect of reduced thickness from other changes, as improvements in DES technology entailed a variety of refinements. In the following sections, the main device features and clinical data for the most commonly used biodegradable polymer DESs are summarized. Figure 1 shows the type and composition of new-generation biodegradable polymer DESs in comparison with early-generation DESs.

Orsiro SES

The Orsiro sirolimus-eluting stent (SES; Biotronik) combines a biodegradable poly(L-lactic acid) (PLLA) polymer with an ultrathin-strut cobalt chromium platform (60 μm for stent diameters up to 3 mm, 80 μm for stent diameters > 3 mm). Sirolimus is eluted over a period of approximately 100 days. The polymer matrix has an asymmetric design that allows for the release of a greater drug dose on the abluminal side than on the luminal side. Four randomized studies have investigated the safety and efficacy of the Orsiro SES: the BIOFLOW-II, BIOSCIENCE, SORT OUT VII, and BIO-RESORT trials.

The BIOFLOW-II trial ($n = 452$) showed the angiographic noninferiority of the Orsiro SES compared with an everolimus-eluting stent (EES) in terms of in-stent late loss at 9 months (0.1 ± 0.32 mm vs 0.11 ± 0.29 mm; P for noninferiority $< .001$).⁶ The BIOSCIENCE trial ($n = 2,119$) demonstrated the noninferiority of the Orsiro SES compared with the Xience EES (Abbott Vascular) for the primary endpoint of target lesion failure at 12 months (6.5% vs 6.6%; P for noninferiority $< .004$).⁷ There was a significant interaction for the primary endpoint favoring the use of the Orsiro SES in patients with ST-segment elevation myocardial infarction.

The SORT OUT VII trial ($n = 2,525$) showed the noninferiority of the Orsiro SES compared with the Nobori biolimus-eluting stent (BES; Terumo Interventional Systems) among all-comer patients undergoing PCI at 12-month follow-up (3.8% vs 4.6%; P for noninferiority $< .004$).⁸ There was a lower rate of definite stent thrombosis among patients randomized to the Orsiro SES group (0.4% vs 1.2%; $P = .03$). The BIO-RESORT trial ($n = 3,514$) showed the noninferiority of the Orsiro SES compared with the Resolute zotarolimus-eluting stent (ZES; Medtronic) with respect to the primary endpoint of target vessel failure (5% vs 5%; P for noninferiority $< .001$).⁹ The finding of a lower stent thrombogenicity with the Orsiro SES has been corroborated by a network meta-analysis of 147 trials ($n = 126,526$) showing a lower risk of stent thrombosis with the Orsiro SES compared with SESs and BESs.¹⁰

Ultimaster SES

The Ultimaster SES (Terumo Interventional Systems) is made of a cobalt chromium platform with thin struts (80 μ m), an open-cell design, and biodegradable poly(DL-lactic acid) and polycaprolactone (PLGA-PCL) polymer applied to the abluminal side. The polymer elutes the drug sirolimus (3.9 μ g/mm stent length), which degrades during a period of 3 to 4 months. In contrast with other biodegradable polymer DESs, the Ultimaster SES features a biodegradable gradient coating, whereby the drug and polymer coating is not present on the stent areas experiencing the highest physical stress—this feature may reduce the risk of polymer cracking and delamination.

The CENTURY II trial ($n = 1,119$) showed the noninferiority of the Ultimaster SES compared with an EES, with freedom from the primary endpoint of cardiac death, target vessel myocardial infarction, and target lesion revascularization in 95.6% and 95.1% of patients allocated to the Ultimaster SES and the EES, respectively (P for noninferiority $< .001$).¹¹ The composite rate of cardiac death and myocardial infarction amounted

to 2.9% and 3.8% ($P = .4$), and target vessel revascularization was 4.5% with the Ultimaster SES and 4.2% with permanent polymer EES, respectively ($P = .77$). The rate of stent thrombosis was 0.9% in both arms.¹¹

Synergy EES

The Synergy EES (Boston Scientific Corporation) is a thin-strut (74–81 μ m), platinum chromium metal alloy platform with an abluminal PLGA polymer, which elutes everolimus (100 μ g/cm²). Three randomized trials have evaluated the angiographic and clinical performance of the Synergy EES: the EVOLVE, EVOLVE II, and BIO-RESORT trials.

The EVOLVE trial ($n = 291$) found the Synergy EES to be noninferior to the Promus Element EES (Boston Scientific Corporation) for the angiographic endpoint of in-stent late lumen loss at 6 months (0.15 ± 0.34 mm for Promus Element, 0.1 ± 0.25 mm for Synergy, and 0.13 ± 0.26 mm for Synergy half; P for noninferiority $< .001$ for all comparisons).¹² The EVOLVE II trial included 1,684 patients undergoing PCI for stable coronary artery disease or non-ST-segment elevation acute coronary syndrome randomized to the Synergy EES or the Promus Element Plus EES. At 12 months, the trial demonstrated the noninferiority of the Synergy EES as compared to the Promus Element Plus EES in an intention-to-treat population with respect to the primary endpoint of target lesion failure defined as cardiac death, target vessel myocardial infarction, and ischemia-driven target lesion revascularization (6.7% vs. 6.5%; P for noninferiority = .0005).¹³ The Synergy EES compared with the Promus Element Plus EES had a similar rate of target lesion revascularization (2.6% vs 1.7%; $P = .21$) and definite or probable stent thrombosis (0.4% vs 0.6%; $P = .5$).¹³ BIO-RESORT was an all-comers trial that featured a 1:1:1 randomization scheme (Orsiro vs Synergy vs Resolute), demonstrated the noninferiority between the Synergy EES and Resolute ZES with respect to the primary endpoint of target vessel failure defined as cardiac death, target vessel-related myocardial infarction, and clinically indicated target vessel revascularization (5% vs 5%; P for noninferiority $< .001$), in addition to the already mentioned noninferiority between the Orsiro SES and Resolute ZES.⁹

MiStent SES

The MiStent SES (Micell Technologies, Inc.) is a cobalt chromium, thin-strut (64 μ m), PLGA-based sirolimus-eluting stent. PLGA carries a crystalline form of sirolimus. The PLGA/sirolimus combination is eluted from the stent within 45 to 60 days, and PLGA is fully absorbed within 90 days. Crystalline sirolimus remains in the tissue and continues to elute into the surrounding tissue for up to

9 months. The DESSOLVE II trial (2:1) reported superiority for in-stent late lumen loss at 9 months for the MiStent SES compared with the Endeavor ZES (Medtronic) (0.27 ± 0.46 mm vs 0.58 ± 0.41 mm; $P < .001$).¹⁴ At 2-year follow-up, the primary endpoint of all-cause death, any myocardial infarction, and clinically driven target vessel revascularization was 6.7% in the MiStent group and 13.3% in the Endeavor ZES group ($P = .17$).¹⁴

Tivoli SES

The Tivoli SES (Essen Technology Co., Ltd.) is a thin-strut (80 μ m), cobalt chromium metal platform with a PLGA polymer, which elutes sirolimus (8 μ g/mm). Approximately 75% of the sirolimus is eluted at 28 days. The I-LOVE-IT 2 trial ($n = 2,737$) reported noninferiority for the primary endpoint target lesion failure at 12 months for the Tivoli SES compared to the durable polymer Firebird SES (Essen Technology Co., Ltd.) (6.3% vs 6.1%; P for noninferiority = .002).¹⁵

Combo SES

The Combo SES (OrbusNeich) is a 100- μ m-thick stainless steel stent covered abuminally with a biodegradable polymer matrix allowing a controlled release of sirolimus. An additional circumferential layer of anti-CD34 antibodies is applied on the stent struts on top of the polymer with the aim of accelerating endothelial coverage. The Combo stent was evaluated in the REMEDEE trial, an angiographic noninferiority study comparing the in-stent late loss at 9 months between the Combo stent and the Taxus Liberté PES in a total of 183 patients (2:1 randomization).¹⁶ The primary endpoint was met, with an in-stent late loss of 0.39 ± 0.45 mm in the Combo group compared with 0.44 ± 0.56 mm in the Taxus Liberté group (P for noninferiority = .0012).¹⁶

CONCLUSION

Available evidence from randomized trials supports an equivalent safety and efficacy profile of thin-strut, biodegradable polymer DESs compared with new-generation, permanent polymer DES. Although most data are available through 1-year follow-up, longer follow-up data suggest that noninferiority is maintained beyond the first year after PCI. Importantly, there is additional evidence that thin-strut, biodegradable DESs may afford improved safety in terms of stent thrombosis compared with thick-strut, biodegradable DESs. As a consequence, biodegradable polymer DESs should not be regarded as a single, homogeneous class, and strut thickness should be factored into the choice of stent selection in clinical practice. Future studies will address whether polymer biodegradation provides additional

benefit to new-generation DESs with permanent polymers at very long-term follow-up. ■

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