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EDITORIAL

Drug-eluting stent technology: progress beyond the polymer

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This editorial refers to 'A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: the CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial'[†], by S. Saito *et al.*, on page 2021.

The polymer matrix represents an integral part of drug-eluting stents (DES) and controls the release of the antiproliferative drug over the course of several weeks to months in order to maximize the anti-restenotic effectiveness. Polymers are applied to the surface circumferentially or only at the abluminal side and can be categorized according to their persistence as permanent or biodegradable. Evidence from histopathological studies of early-generation DES have revealed a chronic inflammatory response to components of the permanent polymer matrix resulting in delayed arterial healing, which has been associated with increased risks of both very late stent thrombosis and late restenosis.[1] Biodegradable polymers have been embraced as a promising development to overcome this limitation.

However, refinements of new-generation DES were not limited to the composition, distribution, and thickness of the polymer, but also extended to the material of the stent platform, its geometry and strut thickness, as well as the selection and dosage of antiproliferative agents. Stent platforms consisting of cobalt–chromium or cobalt–platinum instead of stainless-steel allowed the thickness of stent struts to be reduced by more than half compared with early-generation platforms, while maintaining radial force and stent visibility. Thin-strutted bare-metal stents have been associated with a reduced risk of restenosis.[2] Moreover, experimental data indicate a lower thombogenicity, which may be related to more rapid endothelialization compared with thick-strutted stent types.[3] Antiproliferative substances of the rapamycin family prevailed over paclitaxel in new-generation DES and brought forth several-limus analogues with comparable efficacy.[4] The combined effects of technological progress on different levels translated into improved clinical outcomes, with elimination of previous concerns over very late stent thrombosis, while the anti-restenotic efficacy of early-generation DES have been preserved, and this constitutes the current standard of care.

Several studies have investigated biodegradable polymer DES with permanent polymer early- and new-generation DES (*Table 1*). Final 5 year outcomes of the LEADERS trial corroborated non-inferiority with respect to the primary endpoint (major adverse cardiac events) and demonstrated a reduction of the patient-oriented composite endpoint of all-cause death, myocardial infarction, and revascularization in favour of biodegradable polymer biolimus-eluting Biomatrix stents compared with permanent polymer sirolimus-eluting Cypher stents [35.1 vs. 40.4%, relative risk (RR) 0.84, 95% confidence interval (CI) 0.71–0.98, P for superiority = 0.02].[5,6] Of note, stainless-steel, biodegradable polymer biolimus-eluting Biomatrix stents significantly reduced the rate of very late stent thrombosis between 1 and 5 years in comparison to early-generation, permanent polymer sirolimus-eluting Cypher stents (0.7 vs. 2.5%, RR 0.26, 95% CI 0.10–0.68, $P = 0.003$).[6] In an individual patient data pooled analysis, biodegradable polymer DES based on early-generation stainless-steel platforms have been shown to reduce the risk of stent thrombosis [hazard ratio (HR) 0.56, 95% CI 0.35–0.90] and repeat revascularizations (HR 0.62, 95% CI 0.68–0.98) compared with early-generation, permanent polymer sirolimus-eluting stents during long-term clinical follow-up.[7] Two randomized clinical trials comparing stainless-steel biodegradable polymer biolimus-eluting Nobori stents with a thin-strut, cobalt–chromium permanent polymer everolimus-eluting stent showed non-inferiority with respect to the primary composite endpoint of cardiac death, myocardial infarction and clinically indicated target-vessel revacuariziation (5.2 vs. 4.8%, RR 1.07, 95% CI 0.75–1.52, P non-inferiority <0.0001),[8] and target vessel revascularization (TVR; 4.2 vs. 4.2%, HR 1.01, 95% CI 0.72–1.43) at 12 months, respectively.[9] However, a mixed treatment comparison comparing various biodegradable polymer DES with a thin-strut, cobalt–chromium permanent polymer everolimus-eluting stent suggested that the risk of stent thrombosis (RR 2.04, 95% CI 1.27–3.35) was increased with the former,[10] a finding not confirmed in the direct head-to-head comparisons of NEXT[11] and COMPARE II.[8] Randomized trials investigating biodegradable polymer DES and powered for a clinical endpoint mainly represented stent comparisons across different stent generations (*Table 1*). The novel combination of a

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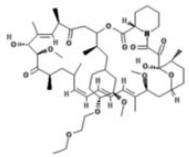
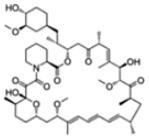
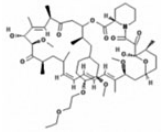
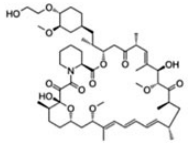
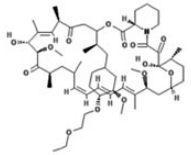
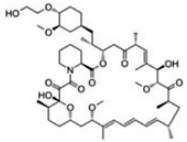
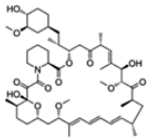
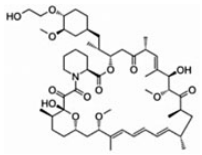
Table 1 Randomized controlled trials with biodegradable polymer stents and primary clinical endpoint

Trial	Study stent	Comparator		Study design (number of patients)	Primary endpoint*	Event rates		Hazard ratio (95% confidence interval)
		Early-generation DES	Newer-generation DES			Study stent	Comparator	
LEADERS[5,6]	***Biomatrix***  Stainless-steel platform 120 μm strut thickness Abluminal PDLLA polymer (10 μm) Biolimus A9 	***Cypher***  Stainless-steel platform 140 μm strut thickness Circumferential PEVA/PBMA polymer (13 μm) Sirolimus 		Non-inferiority ($n = 1707$)	*Cardiac death, MI, clinically-indicated TVR at 9 months Cardiac death, MI, clinically-indicated TVR at 5 years	9.2% 22.3%	10.5% 26.1%	RR 0.88 (95% CI 0.64–1.19) RR 0.83 (95% CI 0.68–1.02)
COMPARE II[8]	***Nobori***  Stainless-steel platform 120 μm strut thickness Abluminal PDLLA polymer (10 μm) Biolimus A9 		***Xience/Promus***  Cobalt–chromium platform 81 μm strut thickness Circumferential PBMA/PVDF-HFP polymer (8 μm) Everolimus 	Non-inferiority ($n = 2707$)	*Cardiac death, non-fatal MI, clinically-indicated TVR at 12 months	5.2%	4.8%	RR 1.07 (95% CI 0.75–1.52)

NEXT[9,11]	***Nobori***  Stainless-steel platform 120 μm strut thickness Abluminal PDLLA polymer (10 μm) Biolimus A9 	***Xience***  Cobalt–chromium platform 81 μm strut thickness Circumferential PBMA/PVDF-HFP polymer (8 μm) Everolimus 	Non-inferiority ($n = 3235$)	*TLR at 12 months TLR at 2 years Death or MI at 2 years	4.2% 6.2% 7.8%	4.2% 6.0% 7.7%	HR 1.01 (95% CI 0.72–1.43) HR 1.04 (95% CI 0.78–1.38) HR 1.02 (95% CI 0.79–1.30)
CENTURY II[12]	***Ultimaster***  Cobalt–chromium platform 80 μm strut thickness Abluminal PDLLA-PCL polymer (15 μm) Sirolimus 	***Xience***  Cobalt–chromium platform 81 μm strut thickness Circumferential PBMA/PVDF-HFP polymer (8 μm) Everolimus 	Non-inferiority ($n = 1123$)	*Cardiac death, TV MI, TLR at 9 months	4.4%	4.9%	2.07% lower limit of one-sided 95% CI

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; PBMA/PVDF-HFP, poly *n*-butyl methacrylate/co-polymer of vinylidine fluoride and hexafluoropropylene; PDLLA, poly-DL-lactic acid; PEVA/PBMA, poly-ethylene-co-vinyl-acetate/poly *n*-butyl methacrylate; RR, relative risk; TLR, target lesion revascularization; TVR, target vessel revascularization; TV MI, target-vessel related myocardial infarction.

biodegradable polymer with a thin-strut cobalt–chromium or cobalt–platinum platform introduces a logical next step in the refinement of biodegradable polymer DES.

The results of the CENTURY II trial published in the current issue of the *European Heart Journal* is the first trial with a primary clinical endpoint to compare thin-strut cobalt–chromium biodegradable polymer DES with the best-in-class new-generation permanent polymer DES.[12] The Ultimaster stent (Terumo, Japan) consists of an 80-μm-thick cobalt–chromium stent coated abluminally with a biodegradable poly-DL-lactic acid (PDLLA) and polycaprolactone co-polymer, which is resorbed within 3–4 months and releases sirolimus. The comparison of two new-generation thin-strut stent platforms with biodegradable and permanent polymer, respectively, rather than a stent comparison across different stent generations, represents a competition on equal grounds and supports the non-inferiority design of the study. In this multicentre study, 1123 patients across Europe, Japan, and South Korea were randomly assigned in a 1:1 fashion to treatment with the new biodegradable polymer, sirolimus-eluting Ultimaster stent or the permanent polymer, everolimus-eluting Xience stent. The study demonstrated non-inferiority of the thin-strut biodegradable polymer, sirolimus-eluting stent with respect to the primary endpoint (target lesion failure) in a largely unselected patient population compared with the permanent polymer, everolimus-eluting stent (4.4 vs. 4.9%, *P* non-inferiority < 0.0001). In a subgroup of patients with angiographic follow-up, in-stent late lumen loss was greater among patients treated with biodegradable polymer, sirolimus-eluting Ultimaster stent compared with those treated with permanent polymer, everolimus-eluting Xience stent (0.26 ± 0.35 vs. 0.18 ± 0.31 mm, $P = 0.003$); however, differences were small in absolute terms, and the finding was not substantiated in rates of in-stent binary restenosis (biodegradable polymer, sirolimus-eluting Ultimaster stent 1.21% vs. permanent polymer, everolimus-eluting Xience stent 1.27%, $P = 0.96$) or in-segment late loss. Complete data monitoring attests to the quality and accuracy of the results, and the angiographic subgroup establishes a solid basis for the potency of the stent. Notwithstanding, the study is inadequately powered for a clinical endpoint trial with a wide non-inferioritiy margin. The presumed event rate of 10% for the composite of cardiac death, target vessel-related myocardial infarction, and target lesion revascularization was considerably higher than the observed rates of target lesion failure. Moreover, the non-inferiority margin of 5.5% is wide in relation to both the expected (10%) and the observed event rates (4.4 and 4.9%, respectively). While the results of the CENTURY II trial support the safety and efficacy of the Ultimaster stent throughout 9 months, potential benefits related to the biodegradable polymer emerging after the time of degradation of the polymer have not been explored and may be available only during long-term follow-up.

An interesting feature of the CENTURY II trial is the combination of regulatory requirements for approval in Japan and Europe, while satisfying an overarching scientific interest of established clinical investigators into the study design. While the potential repercussions of such an integration of regulatory requirements and scientific interests on clinical research remain undetermined at this stage, this approach certainly contributes to expedite global approval of new devices across continents.

Several competing technologies follow a similar strategy of combining biodegradable polymer technology with thin-strut stent platforms. The Synergy stent (Boston Scientific, MA, USA) releases everolimus from an abluminal biodegradable poly-lactic co-glycolic acid (PLGA) polymer applied to a 74-μm-thick platinum–chromium stent platform, which is resorbed during a period of 3–4 months. This stent was found to be non-inferior at 6 months to the permanent polymer everolimus-eluting Promus Element stent in the EVOLVE I study (a randomized comparison with a primary angiographic endpoint) investigating two different doses of everolimus (full-dose 113 μg/20 mm and half-dose 56 μg/20 mm stent surface; results for late lumen loss, full-dose 0.10 ± 0.25 mm vs. half-dose 0.13 ± 0.26 mm vs. Promus 0.15 ± 0.34 mm, *P* non-inferiority < 0.001 for both comparisons).[13] The full-dose platform is currently assessed in the larger scale EVOLVE II trial, powered for clinical endpoints, compared with permanent polymer everolimus-eluting Promus Element stents. The Orsiro stent (Biotronik, Germany) releases sirolimus from biodegradable poly-L-lactic acid (PLLA) applied to a 60-μm-thick cobalt–chromium platform. This stent was found to be non-inferior to the permanent polymer everolimus-eluting Xience stent at 9 months in the randomized Bioflow II study (late lumen loss, 0.10 ± 0.32 vs. 0.11 ± 0.29 mm, *P* non-inferiority < 0.0001).[14] Several ongoing trials powered for clinical endpoints are comparing the Orsiro stent with other new-generation DES. Additional new-generation biodegradable polymer DES using thin-strut platforms include the DESyne BD stent (Elixir, CA, USA), the Combo stent (OrbusNeich, FL, USA), and the MiStent (Micell Technologies, NC, USA).

It remains to be shown whether the late benefit of biodegradable polymers observed with early-generation, thick-strut, stainless-steel stent platforms will translate into a similar benefit with new-generation, thin-strut, cobalt–chromium platforms. Of note, the permanent polymers used in early-generation SES (poly-ethylene-co-vinyl acetate/poly *n*-butyl methacrylate) were modified with new-generation permanent polymer EES (poly *n*-butyl methacrylate/co-polymer of vinylidene fluoride and hexafluoropropylene). Very low event rates observed with new-generation permanent polymer EES beyond 1 year after implantation set the bar high for any competitor, and any difference may be detectable only during very long-term follow-up or in larger patient populations. Alternatively, intracoronary high-resolution imaging modalities, such as optical coherence tomography, may be able to provide more insights into the long-term healing pattern of various stent platforms.[15]

In summary, the Century II trial is one of the first studies to report on outcomes of a newer-generation biodegradable polymer-based DES with thin-strut cobalt–chromium technology, which appears similarly effective during 9 months of follow-up compared with the current gold-standard durable polymer EES. Ongoing studies and longer-term follow-up will determine whether biodegradable polymers in combination with further refinement of stent technology, including ultrathin strut and polymer thickness as well as drug modifications, will further enhance outcomes beyond the excellent results achieved with the present-generation DES.

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