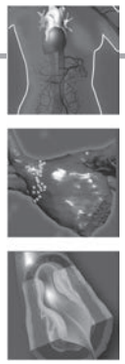

Biodegradable polymer and permanent polymer drug-eluting stents: at the crossroads of evidence and expectation

"…development of new drug-eluting coronary stents with biodegradable polymer coatings will advance with great expectation, yet their clinical adoption will likely be driven more by a formulation of intuition and experience rather than rigorous evidence."

KEYWORDS: angioplasty ■ drug-eluting stent ■ percutaneous coronary intervention

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Against the background of statistically significant and clinically meaningful reductions in clinical restenosis with drug-eluting coronary stents (DES), the persistence of adverse events with first- and second-generation permanent polymer-based DES informs the opportunity for iterative improvement [1–3]. Albeit infrequent, the largely unpredictable observations of acquired stent malapposition, stent thrombosis, progression of neointimal growth or incomplete healing have been demonstrated to be related to patient and lesion complexity, in addition to drug and polymer biocompatibility [4–6]. In particular, long after dissipation of the antiproliferative drug, the persistence of durable polymer coating has been associated with incomplete endothelialization, expansive vessel remodeling, neoatherosclerosis and delayed arterial healing associated with chronic inflammation [7–12]. Biodegradable polymer DES were developed with the purpose of controlling drug release with simultaneous (or subsequent) dissolution of the polymer material, eliminating the stimulus for chronic inflammation and hypothetically restoring the stent phenotype to an inert bare metal stent. Expectedly, the clinical advantage of biodegradable polymer DES would be realized over late-term follow-up – elimination of late stent thrombosis, stability in clinical restenosis and assurances to cease prolonged dual antiplatelet therapy, that in some instances has otherwise been advocated as indefinite treatment following DES revascularization. Despite this potential, benefits specific to biodegradable polymer DES remain intuitive but principally unproven, and the opportunity to demonstrate superiority over existing durable (permanent) polymer DES relative to low-frequency adverse outcomes represents a formidable challenge in clinical trial design.

While distinguished as 'next generation' from permanent polymer DES by construction and composition, design challenges common to both stent types do exist. Similar to durable polymer DES, it is also unlikely that a 'class effect' can be assumed regarding angiographic and clinical outcomes. Variance in polymer formulation and physical properties – for example, hydrophobicity, polymer chain length and crystallinity – determines the temporal course and products of polymer degradation. Monomer and/or acidic byproducts of polymer dissolution have been associated with immunogenicity and vascular inflammation [7,13]. Although the duration of polymer and drug dissolution from the stent surface is commonly described, retention of drug and degradation elements within the arterial wall is often less characterized. Moreover, the selection of antiproliferative drug, the pharmacokinetic release profile and reproducibility of drug elution may yield variable and unpredictable results. As an example, the CoStar II trial demonstrated angiographic and clinical outcomes for a resorbable polymer-based (polylactide-co-glycolide [PLGA]) paclitaxel-eluting stent (CoStar™ Stent, Cordis Corporation, NJ, USA) that were not only inferior to the comparator permanent polymer paclitaxel-eluting stent (TAXUS®, Boston Scientific Corp., MA, USA), but also inconsistent with prior studies involving the same CoStar stent design [14]. In comparison, utilization of the same polymer and similar stent design yet different drug (sirolimus) and elution kinetics (NEVO™, Cordis Corporation) yielded angiographic outcomes that were superior to the TAXUS stent [15].

Accordingly, whether biodegradable polymer DES are as safe (or safer than) and effective as durable polymer DES must be proven for a specific stent type in appropriately designed

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and statistically powered clinical trials. In most instances, recent comparative study of biodegradable and permanent polymer DES has been limited by sample size or observational design, and instead has emphasized angiographic late lumen loss as a measure of biologic efficacy and surrogate for clinical efficacy. In the randomized NEVO RES-ELUTION I trial comparing the NEVO and TAXUS stents (n = 394), the 6-month primary end point of in-stent late lumen loss was significantly lower among patients treated with the NEVO stent (0.13 vs 0.36 mm, p < 0.0001) [15]. Both drug and polymer dissipate from the stent surface by 90 days, conceptually restoring the stent architecture to a bare metal stent. Results were consistent across patient subgroups identified at high risk for restenosis, including diabetes, longer lesion length and smaller reference vessel diameter. Similarly, the EVOLVE trial compared a durable polymer everolimus-eluting stent (PROMUS Element™, Boston Scientific Corp.; n = 98) with two dose formulations of everolimus and PLGA polymer (SYNERGY™, Boston Scientific Corp.; standard dose, n = 94; half dose, n = 99) [16]. Intended to reduce the polymer load and exposure to the vessel, the stent coating is limited to the abluminal surface, and resorption occurs over approximately 4 months. At 6 months, angiographic in-stent late lumen loss was similar for all stent types (PROMUS Element, 0.15 mm; SYNERGY full dose, 0.10 mm; SYNERGY half dose, 0.13 mm; p = 0.56 for comparison), and clinical outcomes did not statistically differ.

Aside from angiographic assessment of neointimal hyperplasia, other studies have included methods of intravascular imaging and measures of vasomotor reactivity that provide insight into temporal patterns and mechanisms of healing otherwise not routinely visible by angiography. In particular, comparative assessment with intravascular ultrasound and optical coherence tomography may identify development of malapposition or aneurysm formation resultant from expansive vessel wall remodeling, characterize the extent and distribution of strut coverage and recognize strut fracture or longitudinal stent distortion. In the OCTDESI study, for instance, 60 patients were randomized evenly to treatment with the TAXUS stent or a biodegradable polymer DES with one of two paclitaxel doses combined with PLGA [17]. Performance of optical coherence tomography imaging at 6 months demonstrated comparable proportions of stent strut coverage and neointimal volume. In the first-in-human DESSOLVE I trial evaluating a stent coated with sirolimus and PLGA with 90-day absorption kinetics, angiographic and intravascular imaging was performed for three separate cohorts (n = 10 per group) at 4, 6 and 8 months to identify potential patterns in healing and neointimal growth [18]. Sample size limitations notwithstanding, the results suggested an early period of near complete strut coverage at 4 months, followed by stability in suppression of neointimal hyperplasia at later durations. Although associated with durable polymer DES [19], whether late progression of neointimal growth within the stent segment also occurs for biodegradable polymer DES is less certain. Among selected patients treated with durable polymer sirolimus-eluting stents (SES) and biodegradable polymer biolimus-eluting stents (BES) undergoing serial intravascular ultrasound examination through 5 years, the temporal course and extent of late neointimal hyperplasia formation was similar for both stent types [20].

> *"...the opportunity to demonstrate superiority over existing durable (permanent) polymer drug-eluting stents ... represents a formidable challenge in clinical trial design."*

Assuming demonstration of clinical efficacy, few studies have formally examined late-term, low-frequency safety outcomes to establish the merits of biodegradable DES beyond concept alone. Among 1707 patients randomized to percutaneous coronary revascularization with either BES with biodegradable polymer or SES with permanent polymer (Cypher, Cordis Corporation), the 4-year composite outcome of cardiovascular death, myocardial infarction or clinically-indicated target vessel revascularization in the LEADERS trial was statistically noninferior between stent types (18.7% BES vs 22.6% SES; relative risk: 0.81; 95% CI: 0.66–1.0; p < 0.001 for noninferiority, p = 0.05 for superiority) [21]. However, occurrence of definite or probable very late stent thrombosis (1–4 years) was significantly less common in the BES cohort (relative risk: 0.29; 95% CI: 0.12–0.73; p = 0.005), a difference that in part contributed to fewer adverse cardiac events over long-term follow-up. In comparison, the ISAR-TEST 4 trial randomized 2603 patients with broad inclusion criteria to treatment with either a sirolimus-eluting biodegradable polymer stent (n = 1299) or permanent polymer DES (SES, n = 652; everolimus-eluting stent, n = 652) [22].

At 3 years, no significant difference was observed between polymer types regarding the combined end point of target lesion failure (cardiovascular death, target vessel-related myocardial infarction or target lesion revascularization: 20.1 vs 20.9%; p = 0.59). Rates of definite or probable stent thrombosis were also similar in both groups (1.2 vs 1.7%; p = 0.32). Trends in late safety and efficacy events (>1 year) were infrequent and comparable between both stent types. Considering the inconsistent results between trials, indeed the benefit of biodegradable polymer DES may be best identified over the long term. In systematic overview of comparative biodegradable and durable polymer DES, no difference in stent thrombosis within the first year of index revascularization is observed [23]; however, when trials with extended follow-up (>1 year) are evaluated, biodegradable polymer DES are associated with a statistically significant 40% relative reduction in stent thrombosis compared with permanent polymer DES [21].

> *"...a critical focus of new drug-eluting stents is to address outstanding dilemmas ... related to abbreviated dual antiplatelet therapy, premature antiplatelet therapy cessation and very late stent thrombosis."*

With limited large-scale trial data, results with biodegradable polymer DES are reassuring but do not conclusively demonstrate superiority over existing standards. Challenging this issue further relies partly on the feasibility of performing randomized clinical trials with appropriate statistical power that permit meaningful demonstration of safety benefit. Revision of trial end points more specific to the stent territory and restrictive statistical modeling further narrows the opportunity to establish clinical equivalence, much less superiority. Perhaps most confounding is that contemporary trials with advanced generation durable polymer DES report the most favorable efficacy and safety outcomes to date, further raising the standard [24,25]. Such practical limitations in trial design, conduct and expense invite even more unanswered questions. Must a new biodegradable polymer DES demonstrate similar effectiveness in direct comparison with existing DES, or is inference enough? Is 'as good' (i.e., noninferiority) with existing durable polymer DES satisfactory, or is superiority a requirement? Are preclinical and mechanistic studies sufficient to justify clinical adoption with otherwise limited clinical experience?

These unresolved issues notwithstanding, the challenge and opportunity for biodegradable polymer DES lies in merging the efficacy associated with current DES with late safety attributed to conventional bare metal stents. To that purpose, rather than demonstration of clinical equivalence alone, a critical focus of new DES is to address outstanding dilemmas in interventional cardiology related to abbreviated dual antiplatelet therapy, premature antiplatelet therapy cessation and very late stent thrombosis. Although seemingly formidable, opportunities do exist for creative trial design that may provide insight to these criteria; how and whether regulatory agencies will interpret results and permit device-specific indications is uncertain. Until then, the development of new DES with biodegradable polymer coatings will advance with great expectation, yet their clinical adoption will likely be driven more by a formulation of intuition and experience rather than rigorous evidence.

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