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

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 (poly-lactide-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 clinical trials.
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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 revascular-
ization 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 ISART-
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].

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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., non-inferiority) 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.

Financial & competing interests disclosure

DE Kandzari receives research and grant support from Abbott Vascular, Boston Scientific and Medtronic CardioVascular; and consulting/advisory board honoraria from Boston Scientific, Medtronic CardioVascular and Micell Technologies. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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