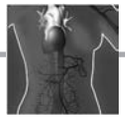
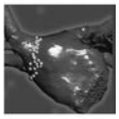
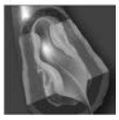

Drug-eluting stents: the next generation

The small but absolute increase in late and very late stent thrombosis associated with drug-eluting stent technology may in part be related to the permanent, durable polymers currently employed with these stent platforms. Research has recently focused on two strategies to combat this problem; bioabsorbable polymers and polymer-free stents. This article critically reviews the key clinical trials and recent conference updates surrounding these two approaches and future directions for technology development.

KEYWORDS: bioabsorbable ■ biodegradable ■ bioresorbable ■ drug-eluting stent ■ polymer ■ stent thrombosis

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Since their introduction, drug-eluting stents (DES) have revolutionized percutaneous treatment of coronary artery disease with rates of in-stent restenosis of between 2 and 10% [1] and significant reductions in target lesion revascularization [2]. However, there has been a small but important absolute increase in rates of late and very late stent thrombosis (VLST) when compared with bare-metal stents (BMS) [3–5]. This increased risk is, in part, due to delayed intimal healing secondary to the antiproliferative drugs employed in current generation stent technology as observed in preclinical [6], human autopsy, angioscopic and more recently optical coherence tomography (OCT) studies [7–9]. However, the phenomenon is likely to be multifactorial in origin. Clinical and procedural risk factors include overlapping stent zones, stent malapposition, premature discontinuation of antiplatelet therapy, cytochrome P450 2C19*2 loss-of-function allelic variation, diabetes and acute coronary syndrome [10–13]. Increasing concern also surrounds the polymers currently used to bind and control release of drug from stents. Nonerodable permanent (or 'durable') polymers, for example polyethylene-co-vinyl acetate and poly n-butyl methacrylate as used in Cypher® and poly(styrene-b-isobutylene-b-styrene) as used in Taxus™, have been shown to illicit vascular hypersensitivity responses in animal models [14]. Expanded characteristics of contemporary permanent polymer DES are listed in Table 1. In addition, damage to the surface integrity of drug-polymer coating has been described during delivery of durable polymer DES, which may represent a nidus for late thrombus formation (Figure 1) [15].

These observations have led to several distinct approaches to combat the problems associated with durable polymers. This article examines the clinical trial evidence and recent conference updates accumulated for (i) bioabsorbable polymers that control the release of drug over the short term, but are designed such that after a variable time they have completely degraded leaving only a BMS, and (ii) polymer-free technology that utilizes unique stent design to control drug release.

Bioabsorbable polymers

It is accepted that polymer breakdown occurs through various mechanisms [16], but for the purpose of this article the exact terminology has been simplified and bioabsorbable will be used to describe all mechanisms of polymer breakdown. Early investigations noted a wide range of vascular inflammatory response to different bioabsorbable polymers [17]. However, in a separate investigation it was noted that high molecular weight poly-L-lactic acid caused no acute or chronic inflammation in porcine coronary arteries [18]. It should also be noted that despite a possible proinflammatory stimulus the polymer will completely degrade within 6–9 months, usually through hydrolysis to leave only a BMS *in situ*. This has subsequently led to large multicenter investigations of next-generation DES utilizing bioabsorbable polymers.

The first large-scale trial to investigate the potential clinical benefit of bioabsorbable polymers was the Cobalt–Chromium Stent With Antiproliferative for Restenosis (COSTAR II) study [19]. The CoStar™ (Conor Medsystems, CA, USA) stent consisted of a cobalt–chromium

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Table 1. Permanent polymer drug-eluting stent characteristics.

DES name	Stent platform	Strut thickness (μm)	Polymer	Antiproliferative drug
Cypher Select®	Stainless steel	140	Polyethylene-co-vinyl acetate and poly (n-butyl methacrylate)	Sirolimus
Endeavor®	Cobalt–chromium	91	Phosphorylcholine	Zotarolimus
Endeavor Resolute®	Cobalt–chromium	91	C19 polymer, polyvinylpyrrolidinone and C10 polymer	Zotarolimus
TAXUS Liberte®	Stainless steel	97	Poly (styrene-b-isobutylene-b-styrene)	Paclitaxel
Xience V™	Cobalt–chromium	81	Poly vinylidene fluoride and hexafluoropropylene copolymer	Everolimus

DES: Drug-eluting stent.

alloy platform with laser-cut reservoirs containing polylactic-co-glycolic acid polymer with the antiproliferative drug paclitaxel. This study randomized 1700 patients to either the CoStar or TAXUS® Express (Boston Scientific Corp. MA, USA) DES. Results were unfortunately disappointing; CoStar failed to meet noninferiority criteria versus TAXUS Express, with significantly higher rates of the 8-month primary end point of major adverse cardiac events (MACE). This was largely driven by a higher rate of target vessel revascularization (TVR) in the CoStar arm (8.1 vs 4.3%; p = 0.002) and higher rates of binary in-stent restenosis, in keeping with a higher 9-month in-segment late loss for CoStar compared with TAXUS Express (0.49 vs 0.18 mm; p < 0.0001) in the angiographic substudy population. However, despite this early setback, research interest has continued to pursue a bioabsorbable polymer DES concept (Table 2).

Thus far, the most comprehensive clinical trial data from commercially available bioabsorbable polymer DES, relate to the stents of the BioMatrix™ family (Biosensors, CA, USA) and the Nobori™ stent (Terumo, Tokyo, Japan). The stent platform is of stainless steel design with quadrature-linkage, with a 50:50 matrix of polylactic acid (PLA) and Biolimus A9™ (a semi-synthetic sirolimus analogue with tenfold greater lipophilicity) applied only to the abluminal stent surface. It is reported that the PLA polymer is completely converted to lactic acid by 6 months and via the Krebs cycle to carbon dioxide and water between 6 and 9 months.

The Limus Eluted from A Durable versus ERodable Stent coating (LEADERS) multicenter noninferiority trial randomized 1707 patients to either the BioMatrix Flex or Cypher Select® stent (Cordis Corp., FL, USA) [20]. The BioMatrix Flex stent was found to be noninferior to the Cypher Select for the composite primary end point of cardiac death, myocardial infarction (MI), or clinically indicated TVR at 9 months (9.5 vs 10.5%; p-noninferiority = 0.003) (Figure 2). In a modest number of patients, the LEADERS OCT substudy reported greater endothelial coverage at 9 months in those receiving BioMatrix Flex compared with Cypher Select [21]. Recently reported 2-year follow-up results confirmed the continued noninferiority of the BioMatrix Flex stent for the composite end point, a significant reduction of the MACE in those with ST elevation MI (8.1 vs 19.3%; p < 0.01) and the absence of VLST following discontinuation of dual antiplatelet activity in the BioMatrix Flex arm [22] independent from the timepoint of discontinuation.

Promising results have also been seen with the Nobori Biolimus A9/PLA stent when compared with the TAXUS Liberté® [23]. The Nobori 1 Phase II trial, which randomized 243 patients to either Nobori or TAXUS Liberté in a 2:1 ratio, found the Nobori to be noninferior for the primary outcome of in-stent late loss at 9 months (0.32 ± 0.50 mm vs 0.11 ± 0.30 mm; p-noninferiority < 0.001). Interestingly stent thrombosis was not demonstrated with the Nobori platform but did occur in 4.4% of TAXUS Liberté patients.

The ongoing Nobori 2, single arm, allcomers' trial, which includes diabetes, acute coronary syndrome, bifurcation and off-label usage, has reported interim analysis from the first 1000 patients, with a major device-related cardiac event (death, MI and target lesion revascularization [TLR]) of under 5% [24]. A total of 3386 patients have now completed 6-month follow-up. The combined stent thrombosis rate is impressively low at 0.14%.

These BioMatrix Flex and Nobori programs represent the largest current pool of randomized patients investigating a novel but commercially available DES with bioabsorbable polymer. Further data will soon be available from the ongoing allcomer e-Biomatrix registry, as well as randomized clinical end point trials comparing Nobori with Cypher and Xience™. Such

data, in addition to defining efficacy, should help give further signal as to whether bioabsorbable polymer strategies do in fact fulfil their promise of reduction in VLST.

The recently published Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST 4) study has added further to the accumulating body of

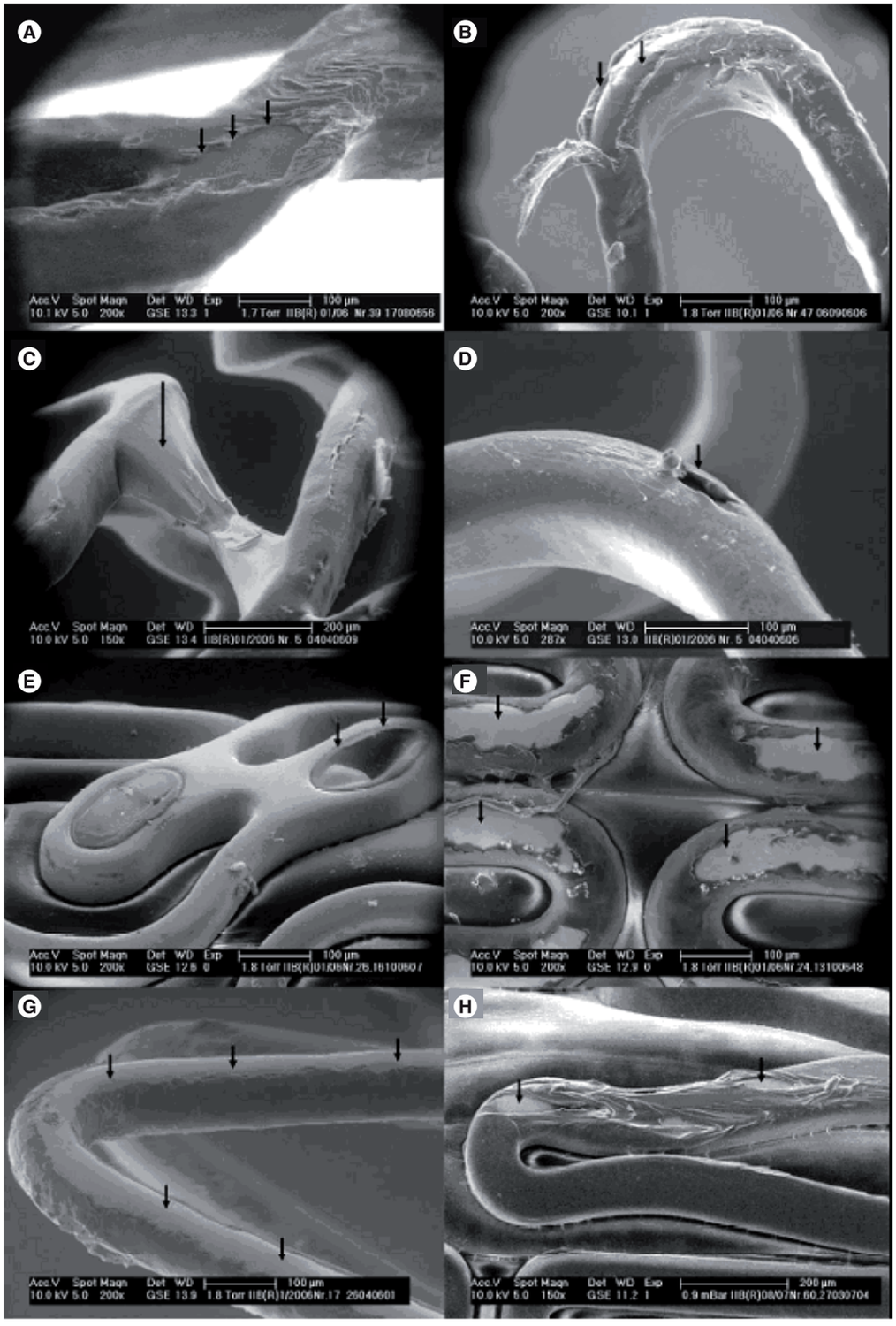

Figure 1. Damage to drug-eluting stent surface integrity after failed deployment.
(A) Cypher Select®, **(B)** Cypher Select, **(C)** TAXUS Liberté®, **(D)** TAXUS Liberté, **(E)** CoStar™ drug-eluting stent (note absence of drug in microwell), **(F)** Endeavor RX®, **(G)** Endeavor RX, **(H)** Xience V™. Reproduced with permission from [15].

Table 2. Key trials investigating bioabsorbable polymer drug-eluting stents.

Stent	Key trials	Patients (n)	Primary end point	Result	Significance
CoStar™ DES	CoStar II	1700	Composite: death, non-Q or Q MI, TVR	CoStar inferior to TAXUS® Express	–
BioMatrix™ Flex	LEADERS	1707	Composite: cardiac death, MI, clinically indicated TVR at 9 months	BioMatrix Flex 9.2% vs Cypher® Select 10.5%	p (noninferiority) = 0.003
Nobori™	Nobori 1 Phase II	243	In-stent late loss	TAXUS® Liberté 0.32 ± 0.50 mm vs Nobori 0.11 ± 0.30 mm	p (noninferiority) < 0.001
	Nobori 2	3074†	Composite: death, MI and TLR	First 1000 patients <5%	–
Yukon® (bioabsorbable)	ISAR Test 4	2603	Composite: death, target vessel MI, TLR	RR: 0.96 (Yukon vs Cypher/Xience)	p = 0.66
Supralimus	Paint Study	274	In-stent late loss 9/12	0.54 ± 0.44 mm (Cypher), 0.32 ± 0.43 mm (Supralimus) vs 0.90 ± 0.45 mm (BMS – Infinium)	p < 0.01
	eSeris Registry	1181†	Composite: death, MI, TLR/TVR	4.5%	–
JACTAX	OCTDESI	60	% uncovered stent struts by OCT 6 months	5.3 (Liberté) vs 4.6 vs 7.0% (LD and HD Jactax)	p = 0.81
NEVO	NEVO RES-Elution 1	364	Late lumen loss	0.13 mm (NEVO) vs 0.36 mm (TAXUS Liberté)	p < 0.001
Elixir Novolimus	FIM	9	In-stent late loss	0.16 ± 0.23 mm	–
Elixir Myolimus	FIM	Group 1: 15 Group 2: 15	In-stent late loss 6/12 In-stent late loss 12/12	0.08 ± 0.16 mm Awaited	–
Biomime™	Preclinical only	NA	NA	NA	–
CardioMind Sparrow™	CARE II	220†	In-stent late lumen loss	Awaited	–

†*Patient recruitment and enrollment not completed.*
BMS: Bare-metal stent; CARE: CardioMind Sparrow DES system; DES: Drug-eluting stent; FIM: First-in-man; HD: High-dose; ISAR: Intracoronary stenting and angiographic results; LEADERS: Limus Eluted From A Durable Versus Erodable Stent Coating; LD: Low-dose; MI: Myocardial infarction; NA: Not applicable; OCTDESI: Optical Coherence Tomography Drug Eluting Stent Investigation; TLR: Target lesion revascularizaton; TVR: Target vessel revascularization.

evidence with regard to bioabsorbable polymer technology [25]. This study utilized a 316L sand-blasted microporous stainless steel stent (Yukon®), which was coated on-site with a mixture containing rapamycin, biodegradable polymer and shellac resin [26]. In total, 2603 patients were randomized to either the novel DES, a Cypher (sirolimus) or a Xience (everolimus; Abbot, IL, USA) DES. The novel DES was found to be noninferior to the Cypher/Xience arm for the primary composite end point of cardiac death, MI related to the target vessel and TLR at 12 months. The incidence of definite and probable stent thrombosis was not significantly different although much longer follow-up is required to assess whether or not a signal towards reduced VLST is emerging (Figure 3).

The Indian manufacturer Sahajanand (Gujarat, India) presented initial results of their bioabsorbable polymer platform – the Supralimus DES – at TCT09 [27]. Based on the stainless steel Matrix® stent, Sahajanand have applied a copolymer consisting of poly-L-lactide, polyvinyl pyrollidone, poly-lactide-co-caprolactone and polylactide-co-glycolide. This results in biphasic release of sirolimus with 50% elution by day 9 and 100% elution by day 48. The polymer has completely degraded by 7 months. The Seris 1 nonrandomized study reported, in 100 patients, an in-stent late-loss of only 0.09 ± 0.28 mm at 6 months and no definite stent thrombosis at the 30-month follow-up [28]. This encouraging result led to the subsequent Percutaneous Intervention with Biodegradable-Polymer Based Paclitaxel-Eluting or Sirolimus-Eluting versus Bare Stents (PAINT) study, which randomized 274 patients to either a Supralimus stent, an Innfinium™ paclitaxel-eluting DES or a BMS [29]. PAINT demonstrated superiority ($p < 0.01$) for the two DES platforms investigated with respect to the primary end point of in-stent late loss at 9 months when compared with BMS (although there was no statistical difference between the Supralimus and Innfinium DES: Supralimus 0.32 ± 0.43 mm; Innfinium 0.54 ± 0.44 mm; BMS 0.90 ± 0.45 mm). The subsequent eSeris registry confirmed the initial clinical data in a real world population of 1181 patients in which the rate of definite/probable stent thrombosis was 0.5% with only 2.0% TLR/TVR. The proposed Seris 3 noninferiority study plans to randomize patients to Supralimus or the Xience V stent as a contemporary comparator.

Boston Scientific has recently reported the results of the Optical Coherence Tomography Drug Eluting Stent Investigation (OCTDESI) trial; part of the JACTAX stent program [30]. The JACTAX stent consists of a Liberté™ stent platform with an abluminal coating of bioabsorbable polylactide polymer and paclitaxel. The microdot coating of polymer–drug matrix, in addition to its abluminal-only application, results in much lower concentrations of both the polymer and the drug being required on the stent, as well as the theorectical safety advantage of a nonpolymer-coated luminal surface. The focus of OCTDESI was to test this hypothesis by assessing intimal healing and the surrogate marker of percentage stent strut coverage by OCT. Patients were randomized to both low dose and high dose JACTAX DES versus TAXUS Liberté, with the primary end point being the percentage of uncovered stent struts at 6 months. Enrolling only 60 patients in total, this small study was not able to find a difference in the primary end point between the three stent platforms; however, there were no stent thromboses observed with the JACTAX arms, and late lumen loss was comparable to TAXUS Liberté, thus supporting further evaluation of this stent platform in larger groups of patients.

The innovative Nevo™ stent system (Cordis Corp., FL, USA) comprises a cobalt–chromium stent platform incorporating multiple microwells that contain a matrix of poly(lactide-co-glycolide; PLGA) bioabsorbable polymer and sirolimus. It must be noted that the stent platform has been completely redesigned from the CoStar bare metal platform on which the microwell technology is based [31]. This system potentially improves safety through reduction of the contact area between vessel wall and polymer by 75%, and enables 80% sirolimus release by 30 days. The Nevo RES one trial randomized 394 patients to either the Nevo or TAXUS Liberté stent [32]. The trial was designed on a noninferiority basis, with a secondary superiority analysis if noninferiority was confirmed for the primary end point of late lumen loss. At 6-month follow-up, the mean late lumen loss in the Nevo arm was significantly lower than with TAXUS Liberté (0.13 vs 0.36 mm; $p < 0.001$). In addition, one probable and one possible stent thrombosis were observed with the TAXUS Liberté arm whereas no stent thromboses were observed in the Nevo arm. Large-scale randomized trials and registries are now ongoing.

Elixir Medical (CA, USA) reported several first-in-man studies at TCT09 using a cobalt alloy stent platform with bioabsorbable polylactide polymer and either novolimus (5 µg/mm) or myolimus (3 µg/mm) as the antiproliferative agent.

A first-in-man single-arm multicenter registry of the Elixir/Novolimus stent in nine patients demonstrated in-stent late loss of 0.16 ± 0.23 mm with no MACE [33]. Further investigation is planned. A multicenter registry of the Elixir/Myolimus stent [34], reported in-stent late-loss of only 0.08 ± 0.16 mm at 6 months in 15 patients. The 12-month quantitative angiographic (QCA) results of a parallel group of patients are awaited.

The Biomime™ stent (Meril, Gujarat, India) is based on the CE marked NexGen™ cobalt–chromium stent, which has a unique electropolished surface and very low stent strut thickness (65 µm) with the aim of improving laminar blood flow, flexibility, conformability and trackability. To this platform, a matrix consisting of a custom biodegradable polymer (a combination of PLA and PLGA) and sirolimus at a concentration slightly lower than that on Cypher (1.25 vs 1.4 µg/mm^2) resulting in slightly lower tissue concentration. Similar to Cypher, the release profile enables over 80% drug elution by day 30. A clinical registry of the Biomime DES including mandatory 8-month angiographic follow-up

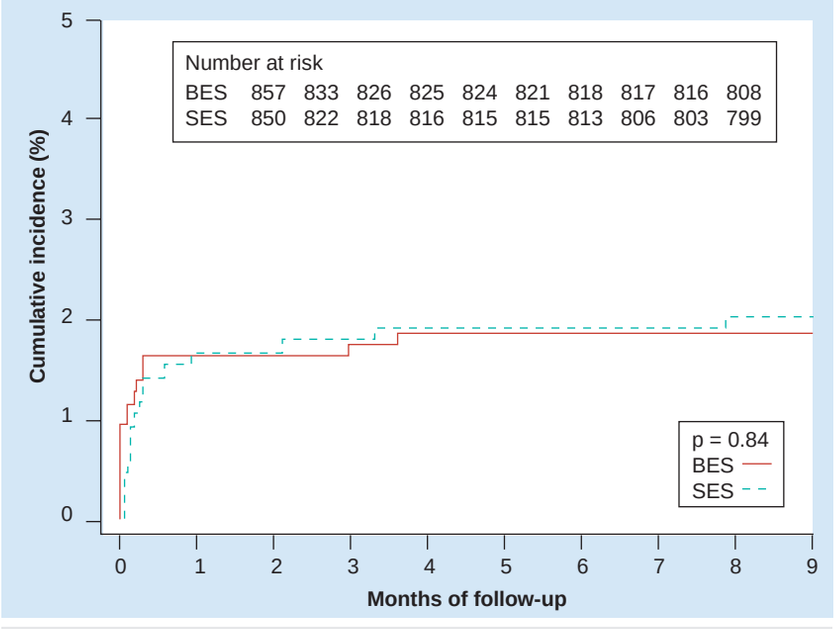

Figure 2. Time to event curves for definite stent thrombosis with BioMatrix™ Flex versus Cypher Select® in the Limus Eluted From A Durable Versus Erodable Stent Coating (LEADERS) trial.
BES: Biolimus-eluting stent; SES: Sirolimus-eluting stent.
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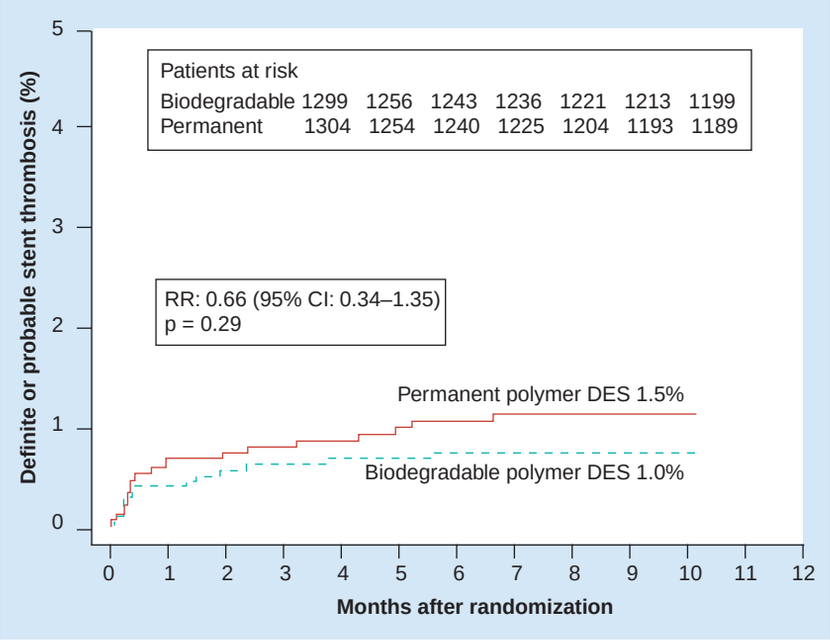

Figure 3. Time to event curve for definite/probable stent thrombosis in the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST 4) study.
p-value is two-tailed from superiority testing.
DES: Drug-eluting stent.
Reproduced with permission from [25].

in 250 patients from multiple Indian centers is planned, the results of which will guide design of further head-to-head studies [35].

The innovative solution to small vessel stenting – the Sparrow™ 'stent in a wire' system (CardioMind, CA, USA) with its battery-released, self-expanding, ultra-thin strut nitinol stent, also includes a bioabsorbable PLA/PLGA copolymer coating and sirolimus (6 µg/mm). The ongoing CardioMind Sparrow™ DES system (CARE II) trial aims to randomize up to 220 patients to the Sparrow DES, Sparrow bare metal and a propriety cobalt–chromium stent (Microdriver®/Driver®) [36]. Encouraging feasibility data were recently presented from the initial 100 patients with 8-month data expected mid-2010.

Polymer-free drug delivery

Local drug delivery from an implanted stent, without the need for a polymer, represents a further potential enhancement in safety and not only over the longer term but also, depending on the release kinetics, during the early postdeployment phase. Several novel methods have been investigated including nanowells, micropores and abluminal grooves (Table 3).

One of the earliest polymer-free designs was the Janus flex stent (Sorin, Italy), later known as the Optima stent (carbostent implantable devices). This 316L stainless steel stent, has a passive coating of Carbofilm™ (turbostatic carbon coating), which may promote neointimal healing [37], and engineered grooves on its abluminal surface that function as drug reservoirs for tacrolimus, the release of which is controlled by simple diffusion into the vessel wall. A small randomized trial comparing the Janus flex with the Tecnic BMS reported a significant reduction in MACE with the Janus stent (6 vs 15%; p = 0.038) driven primarily by a reduction in TLR (6 vs 13%; p = 0.059 [38]. Interestingly, the direction of recent research with the Janus flex/CID Optima® has been focused on the potential safety of short duration dual antiplatelet therapy (DAPT), the hypothesis being that without polymer, the need for DAPT will be reduced [39]. The Matrix 1 registry has demonstrated apparent clinical safety of DAPT for only 2 months, reporting no significant difference in MACE between patients taking 2 or 6 months DAPT, both groups being well-matched with regard to baseline characteristics, including a significant proportion with acute coronary syndromes in each group. Stent thrombosis was only observed in 0.17% of the whole cohort. However, it must be cautioned that this finding was at only 12 months of follow-up and the study was underpowered to show a difference in-stent thrombosis events, given the very low incidence in both groups. Ongoing studies with the Optima stent include the warfarin (WAR) stent study investigating 2 months DAPT in patients taking warfarin, the Matrix II registry, and the Brazilian Evaluation of Safety Using Tacrolimus-Eluting Stent (BEST) study investigating the safety of only 2 months of DAPT.

In addition to their bioabsorbable polymer stent, Biosensors have developed a polymer-free system, termed BioFreedom™. This uses a 316L stainless steel stent with a novel surface modification, creating a microporous reservoir on the abluminal surface to control release of the antiproliferative agent Biolimus A9. While 90% of drug is released after only 50 h, due to the high lipophilicity of Biolimus A9 (~10x greater than that of sirolimus), there is still a significant concentration of the drug in tissue surrounding the stent at 28 days. By 90 days, this has reduced to a negligible level. A first-in-man randomized trial (n = 75 patients) comparing BioFreedom (standard dose or low dose) with TAXUS Liberté (in 1:1:1 ratio) reported the primary end point of in-stent late loss at 6 months to be significantly lower in both standard and low-dose BioFreedom stents (0.08 and 0.12 mm, respectively) compared

Table 3. Key trials investigating polymer-free drug-eluting stents.

Stent	Key trials	Patients (n)	Primary end point	Result	Significance level
CID Optima®	Matrix 1 registry	572	Acute, subacute and late stent thrombosis	Overall 0.17% stent thrombosis with no late thrombosis seen (12/12 fu)	NA
BioFreedom™	BioFreedom™ FIM	75	In-stent late loss	SD 0.08 mm; LD 0.12 mm vs TAXUS® Liberté 0.37 mm	p = 0.0001; p = 0.002
Amazonia Pax®	Pax A	30†	Percentage of neointimal hyperplasia obstruction	NA	NA
	Pax B	100†	In-stent late lumen loss	NA	NA
Nile Pax®	BiPax	100†	Angiographic binary restenosis	NA	NA
Yukon® (polymer-free)	ISAR Test 2	1007	Angiographic restenosis	12% (Yukon®) and 11% (Cypher®) vs 19.3% (Endeavor®)	p = 0.002

†Patient recruitment and enrollment not completed.
FIM: First-in-man; LD: Low-dose; NA: Not applicable; SD: Standard dose.

with TAXUS Liberté (0.37 mm; <0.0001 and p < 0.002) [40]. No stent thromboses were observed in any arms and MACE were not significantly different.

Utilizing a different polymer-free technique, Minvasys have developed both a conventional DES (the Amazonia®-PAX system) and a dedicated bifurcation stent based on a very thin strut (78 µm) cobalt–chromium platform (NILE®-PAX). In both, the abluminal stent surface is coated in paclitaxel using a microdrop spray crystallization process resulting in a semi-crystalline coating of paclitaxel at a concentration of 2.5 µg/mm^2, which is significantly lower than the concentration observed with the TAXUS Liberté. Complete drug elution is achieved, leaving only bare metal by day 45.

Enrollment into two Amazonia-PAX studies, the randomized PAX A and registry PAX B studies has commenced [41]. PAX A is aiming to randomize 30 patients to the Amazonia-PAX or TAXUS Liberté with the assessment of neointimal hyperplasia assessed with intravascular ultrasound, OCT and QCA at 4 months. The PAX B registry plans to recruit 100 patients and assess angiographic late lumen loss at 9 months.

The BiPAX study, with the NILE-PAX device, plans to recruit 100 patients with bifurcation disease, for 9 months with angiographic assessment for binary restenosis [42]. Approximately a quarter of patients have been shown to need additional sidebranch stenting. Final results of this study and the Amazonia program are expected in 2010.

The ISAR test group has also looked at polymer-free technology with their Yukon stent platform. Initial results from the ISAR-TEST study in 2006 were favorable [43]. Patients were randomized to either the Yukon polymer-free rapamycin-eluting stent or the TAXUS Express DES. The study was designed to demonstrate noninferiority of the Yukon DES for the primary end point of in-stent late lumen loss in 364 patients; the two groups being well balanced for baseline characteristics. At 9-months follow-up there was no difference between the groups for the primary end point (0.48 ± 0.61 vs 0.48 ± 0.58; p = 0.98) and, although a significant proportion of enrolled patients in both groups did not undergo follow-up angiography (19%), sensitivity analysis indicates that the potential for bias from this potential confounder is highly unlikely.

More recently, the ISAR group has investigated a dual-drug, polymer-free, DES utilizing both sirolimus and the antioxidant Probucol [44–47]. The ISAR test 2 trial randomized 1007 patients to either the dual-drug, polymer-free Yukon DES or either Cypher or Endeavor® (Medtronic Inc., MN, USA) in a 1:1:1 balanced randomization. The primary end point of angiographic restenosis was significantly lower in the dual DES and Cypher groups when compared with the Endeavor (12 and 11 vs 19.3%; p = 0.002), and clinical restenosis was less frequent. In addition, overall safety of the dual DES was similar to that of Cypher and Endeavor with no differences in rates of death, MI or definite stent thrombosis. The ISAR TEST 5 study plans to randomize approximately 3000 patients to either the dual polymer-free Yukon DES or the Endeavor Resolute stent [48], aiming to show superiority for the dual-drug strategy with respect to death, MI and TLR at 12 months. It is worth noting that, even if superiority is obtained, it is unclear whether this study will clarify whether it is the addition of Probucol or the lack of polymer within the stent platform that is responsible for possible improvements in stent performance.

Conclusions

The last 12 months have seen continuing research activity into novel biodegradable polymer and polymer-free DES. As this article has highlighted, many studies that have reported, or that are in the process of recruitment, focus on the issue of comparability with current generation DES with regard to their clinical efficacy, namely in-stent restenosis. Noninferiority was confirmed for the BioMatrix Flex stent compared with Cypher Select from the largest pool of evidence comparing a bioabsorbable and a durable polymer stent. Furthermore the 2-year ST segment elevation myocardial infarction subgroup data reported superiority of the BioMatrix Flex for the combined primary end point. This is certainly an interesting and hypothesis-generating finding that may indicate an efficacy advantage for the BioMatrix flex stent platform and/or the Biolimus A9 drug, or may hint at an emerging safety advantage of bioabsorbable polymer in this setting. The 3-year data from the LEADERS trial, anticipated at TCT10, may illuminate this further.

We must also remember that the basic premise on which polymer removal is based is that, through reduced inflammation and improved intimal healing, stent thrombosis rates will be reduced. However, due to relative infrequency of stent thrombosis (just over 1% with current DES platforms [49]), adequately powering a randomized trial to confirm this hypothesis is extremely difficult. Thus, while registry data cannot be considered to provide the same level of evidence as randomized trials, nevertheless the many multicenter registries underway for next generation DES are critically important as they may give early insight into possible reduction or otherwise in stent thrombosis. As we have already seen there is a possible signal of reduced stent thrombosis from the LEADERS 2-year data comparing the BioMatrix Flex stent to the Cypher Select stent. Outcomes of ongoing randomized trials and large registries for both bioabsorbable polymer systems and polymer-free systems are thus eagerly anticipated.

Future perspective

Given the relatively low incidence of VLST with later generation durable polymer stents such as that demonstrated in SPIRIT IV [50], the utility of bioabsorbable polymer technologies will be best tested in clinical settings of highest thrombotic risk. Thus, to provide more definitive evidence of safety, future studies should focus on scenarios such as early discontinuation of antiplatelet therapy (e.g., to facilitate early noncardiac surgery), multiple overlapping stents, tortuous calcified anatomy and prothrombotic patient milieu.

The optimization of polymer-free DES and clinical introduction of fully bioabsorbable stents is likely over the medium term, although definitive large-scale randomized and registry data are still awaited. Such developments may ultimately be complimentary to, rather than replacements for, current devices. Increasingly, a more comprehensive understanding of individual patient risk will enable tailoring of the appropriate device to the appropriate patient.

Executive summary

Background

- Drug-eluting stents (DES) result in a small but significant increase in late and very late stent thrombosis compared with bare-metal stents.
- This is multifactorial in origin relating to several clinical, procedural and device-related factors.
- Permanent 'durable' polymers used in current generation DES have been shown to delay intimal healing and elicit vascular hypersensitivity responses thought to be significant initiators of stent thrombosis.

Bioabsorbable polymers

- Although initial trials with the bioabsorbable polymer CoStar™ DES were disappointing, significant advances in bioabsorbable polymer DES development have been achieved.
- A large body of favorable clinical evidence now exists for several bioabsorbable polymer DES platforms including the BioMatrix™ Flex, Nobori and Intracoronary Stenting and Angiographic Results (ISAR) programs.
- Several studies have now shown comparable/improved efficacy of these novel platforms compared with current DES, with possible emerging signals of reduced stent thrombosis and major adverse events in certain subgroups.

Polymer-free DES

- Similarly, while initial results with polymer-free drug delivery technology were unremarkable, recent data have been highly promising and several large randomized and registry-based studies are underway.

Conclusions

- Large studies and registries in high-risk patients will be essential to adequately test the true clinical value of these novel technologies and their ability to reduce stent thrombosis.

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