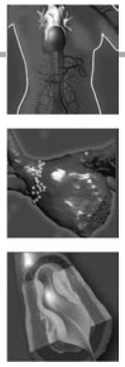

Biodegradable polymer limus-eluting stents are noninferior to permanent polymer-based stents: the ISAR-TEST-4 trial

Biodegradable polymer drug-eluting stent (DES) platforms have the potential to enhance long-term clinical outcomes following coronary stenting. The concept of controlled drug elution by means of a polymer that, subsequent to serving its useful function, degrades to inert monomers is inherently attractive, although data concerning their efficacy are limited to date. In the Intracoronary Stenting and Angiographic Restenosis Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST)-4 study, we hypothesized that at 12 months, clinical safety and efficacy with a biodegradable polymer DES would be noninferior to that of permanent polymer DES. Patients were randomly assigned to treatment with biodegradable polymer DES (sirolimus-eluting; n = 1299) or permanent polymer DES (n = 1304; sirolimus-eluting, Cypher, n = 652; or everolimus-eluting, Xience-V, n = 652). The primary end point was a composite of cardiac death, myocardial infarction related to the target vessel or revascularisation related to the target lesion. The principle finding was that the biodegradable polymer DES was noninferior to permanent polymer DES concerning the primary end point (13.8 vs 14.4%, respectively, p-noninferiority = 0.005; relative risk: 0.96, 95% CI: 0.78–1.17, p-superiority = 0.66).

KEYWORDS: biodegradable ■ coronary restenosis ■ drug-eluting stent ■ polymer ■ sirolimus

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Background & rationale

Over time, it has become clear that despite their dramatic success in tackling coronary restenosis, first generation drug-eluting stents (DES) are associated with a small but significant excess of adverse events late after stent implantation (>12 months), in particular, late stent thrombosis and delayed loss of antirestenotic efficacy [1–4]. The central process underlying these events is delayed healing of the stent segment – a process that is characterized by delayed endothelialization, persistent fibrin deposition and chronic arterial wall inflammation [5,6].

The etiology of delayed arterial healing is undoubtedly multifactorial and at times the definitive dissociation of drug and polymer effects can be difficult [5]. A number of preclinical studies demonstrate increasing arterial wall inflammatory responses late after index intervention [7–9]. At this time point the active drug is completely eluted (at least in limus agent stents) and ongoing inflammatory response to durable polymer residue appears to be the dominant pathology [5]. The time course of adverse events in human autopsy and clinical studies also appear to indicate that polymers rather than drugs are more likely to be the trigger for persistent inflammation and subsequent stent thrombotic events [10,11].

■ ISAR stent project

The Individualizable Drug-Eluting Stent System to Abrogate Restenosis (ISAR) stent project seeks to investigate novel DES coatings yielding a high antirestenotic efficacy without recourse to permanent polymer (**Table 1**) [12–19]. Previous experience revealed that while a completely polymer-free microporous DES platform effectively reduced restenosis [14], the constraints imposed on drug-release control by total absence of carrier polymer resulted in an antirestenotic performance that was not noninferior to currently available gold-standard DES platforms [15,20]. Options to enhance the antirestenotic efficacy of platforms devoid of permanent polymer include the addition of a second drug targeted at another element of the restenotic response cascade or the employment of a self-degrading carrier polymer.

■ Biodegradable polymer stent technology

Biodegradable polymer coatings represent an inherently attractive middle ground in marrying the need for control of drug-release kinetics with the removal of the long-term sequelae of polymer residue. The composition of these polymers is such that they permit control of active drug release over the critical initial 30–60 days before subsequently degrading to inert

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Table 1. The Intracoronary Stent to Abrogate Restenosis (ISAR stent) project clinical trial program: completed and ongoing clinical trials.

	Patients (n)	Investigative stent platforms†	Comparator stent platforms	Ref.
ISAR dose-finding study	602	Polymer-free SES	Bare-metal stent	[7]
ISAR-TEST	450	Polymer-free SES	Permanent polymer PES (Taxus)	[8]
ISAR-TEST-2	1007	Polymer-free dual-DES (sirolimus- and probucol-eluting)	Permanent polymer – SES (Cypher) and – ZES (Endeavor)	[9]
ISAR-TEST-3	605	Polymer-free SES and biodegradable polymer SES	Permanent polymer SES (Cypher)	[10]
ISAR-TEST-4	2603	Biodegradable polymer SES	Permanent polymer – SES (Cypher) and – EES (Xience-V)	[11]
ISAR-TEST-5 (ongoing)	3000	Polymer-free dual-DES (sirolimus- and probucol-eluting)	Permanent polymer ZES (Resolute)	[101]
ISAR-TEST-6 (ongoing)	2010	Biodegradable polymer DES – ISAR SES – Nobori BES	Permanent polymer EES (Xience-V)	[102]

†Investigative stent platforms consist of a sand-blasted, 316 L stainless steel microporous stent backbone (produced by Translumina, Germany), which is coated on site with specific combinations of drug(s) and/or polymer. A detailed description for creating the micropores and its rationale, the specifics of the coating process and the drug-release profile of the individual platforms have been reported previously [7,10,12,13].
BES: Biolimus-eluting stent; DES: Drug-eluting stent; EES: Everolimus-eluting stent; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

monomer fragments, carbon dioxide and water over the course of weeks to months (depending on composition specifics). The promise of this technology has seen a large number of biodegradable polymer DES devices come to clinical testing in the last 1–2 years [15,21–25], although only two prior studies had published results in large patient numbers – the ISAR-TEST-3 (n = 605) [15] and the Limus Eluted From a Durable Versus Erodable Stent Coating (LEADERS; n = 1707) trials [21].

In view of the overall favorable net risk:benefit ratio with first-generation DES and the widespread experience with this technology, demonstration of clinical equivalence to these older devices is imperative before a switch to newer-generation platforms can be contemplated. Following this, long-term follow-up of appropriate patient numbers will enable adjudication on whether the promise of biodegradable technology lives up to expectation.

Trial summary

■ Study design

Full details of the ISAR-TEST-4 study protocol and design are available in the primary manuscript [16,26]. In brief, patients older than 18 years of age with ischemic symptoms or evidence of myocardial ischemia in the presence of 50% or more *de novo* stenosis located in native coronary vessels were enrolled. Patients with a target lesion located in the left main stem or in cardiogenic shock were excluded. The population enrolled is reflective of routine clinical practice at the enrolling institutions where the overwhelming majority of patients consent to participation in randomized clinical trials. Patients were randomly assigned in a 2:1:1 allocation to receive:

- Biodegradable polymer DES (sirolimus-eluting ISAR stent)
- Permanent polymer DES (either sirolimus-eluting; Cypher [Cordis, FL, USA]; n = 652; or everolimus-eluting; Xience-V [Abbott Vascular, IL, USA]).

The biodegradable polymer stent platform consists of a thin-strut (87 µm), microporous 316 L stainless steel stent (Table 1), which is coated on-site with a mixture of sirolimus, biodegradable polymer and shellac resin (a biocompatible resin widely used in the coating of medical tablets). No primer surface is employed and the biodegradable polymer matrix used is completely degraded within 6–9 weeks. The sirolimus concentration utilized is approximately 180 mg/cm^2. Detailed elution characteristics of this stent are reported elsewhere [15,18].

The primary end point of the study was a hard clinical end point – a device-orientated composite of cardiac death, myocardial infarction (MI) related to the target vessel and target lesion revascularization (TLR) at 12 months postindex intervention [19].

■ Data analysis

The objective of the study was to assess the noninferiority of biodegradable polymer DES compared with permanent polymer DES. It

was estimated that with a sample size in each group of 1237, a two-group large-sample normal approximation test of proportions with a one-sided 0.05 significance level and a margin of noninferiority of 3% would have 80% power to reject the null hypothesis in favor of the alternative hypothesis, assuming that the incidence of the primary end point in both groups was 10%. To allow for loss at follow-up, it was planned to enrol 1300 patients in each group.

■ Results

A total of 2603 patients were enrolled and randomized to receive biodegradable polymer DES (n = 1299) or permanent polymer DES (n = 1304; Cypher, n = 652 and Xience, n = 652). Baseline patient and lesion characteristics were similar between the two groups (selected characteristics are shown in Table 2). Follow-up at 1-year was complete on all but 80 patients (3.1%). Follow-up angiography at 6–8 months was performed in 78% of patients in both treatment groups (p = 0.94).

With respect to the primary end point of the trial – cardiac death/MI related to target vessel/TLR – the biodegradable polymer DES was noninferior to permanent polymer DES (13.8 vs 14.4%, respectively, p-noninferiority = 0.005; relative risk: 0.96, 95% CI: 0.78–1.17, p-superiority = 0.66; Figure 1).

Rates of TLR were similar with both stents (8.8 vs 9.4%; p = 0.58). Regarding safety end points, the biodegradable polymer DES in comparison with permanent polymer DES showed similar rates of cardiac death or MI related to target vessel (6.3 vs 6.2%, respectively; relative risk: 0.97; 95% CI: 0.74–1.28; p = 0.94; Figure 2). The rate of definite/probable stent thrombosis at 1 year was similar with the biodegradable polymer DES in comparison with permanent polymer DES (1.0 vs 1.5%, respectively; relative risk: 0.68; 95% CI: 0.34–1.38; p = 0.29; Figure 2); nor were there any differences in event rates at 30 days (0.5 vs 0.8%, respectively; relative risk: 0.61; 95% CI: 0.18–1.82; p = 0.32).

In terms of subgroups there was no signal of performance difference between the biodegradable polymer DES and the individual component groups of the permanent polymer DES: rate of cardiac death/MI related to target vessel /TLR with biodegradable polymer DES: 13.8 versus Cypher: 15.2% (relative risk: 0.90; 95% CI: 0.71–1.16; p = 0.43) and versus Xience-V 13.6% (relative risk: 1.01; 95% CI: 0.78–1.31; p = 0.94).

Table 2. Selected baseline characteristics.

	Biodegradable polymer DES (n = 1299)	Permanent polymer DES (n = 1304)	p-value
Patient			
Age	66.7 ± 10.7	66.8 ± 11.1	0.79
Male	978 (75.3)	1002 (76.8)	0.35
Diabetes mellitus	376 (29.0)	377 (28.9)	0.99
– Insulin-dependent	108 (8.3)	122 (9.4)	0.35
Prior myocardial infarction	372 (28.6)	373 (28.6)	0.99
Multivessel disease	1124 (86.5)	1126 (86.3)	0.89
Clinical presentation			0.24
– Acute myocardial infarction	167 (12.9)	140 (10.7)	
– Unstable angina	374 (28.8)	379 (29.1)	
– Stable angina	758 (58.4)	785 (60.2)	
Multilesion intervention	375 (28.9)	340 (26.1)	0.11
Prior bypass surgery	129 (9.9)	129 (9.9)	0.97
Lesion			
Chronic total occlusion	86 (5.1)	89 (5.3)	0.80
Bifurcation	421 (25.0)	383 (22.7)	0.11
Ostial	267 (15.9)	304 (18.0)	0.10
Complex morphology (B2/C)	1225 (72.8)	1218 (72.1)	0.66
Lesion length	14.8 ± 8.6	15.0 ± 8.8	0.53
Vessel size	2.79 ± 0.47	2.80 ± 0.52	0.67

Data are shown as mean ± standard deviation or number (percentage).
DES: Drug-eluting stent.

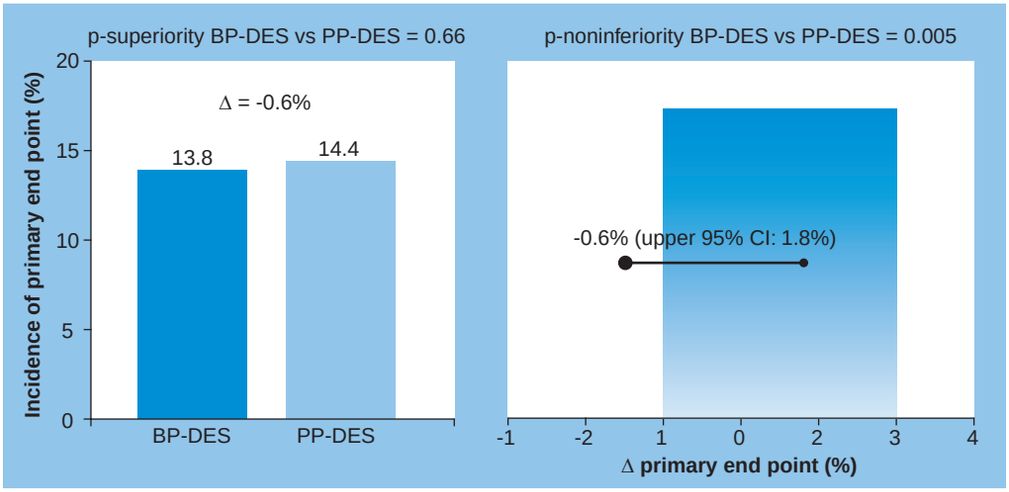

Figure 1. Incidence of the primary end point of cardiac death, myocardial infarction related to the target vessel or revascularization related to the target lesion for biodegradable polymer and permanent polymer DES.
BP-DES: Biodegradable polymer drug-eluting stent; PP-DES: Permanent polymer drug-eluting stent.

Conclusion

In this large-scale randomized trial, we found that a biodegradable polymer sirolimus-eluting stent was not inferior to permanent polymer DES in a large-scale study powered for a composite clinical safety and efficacy end point. Furthermore, at 1 year there was no sign of difference between biodegradable polymer DES and permanent polymer DES regarding individual efficacy (i.e., TLR) or safety (cardiac death/MI or stent thrombosis) end point components. This demonstration of noninferiority provides a platform for testing the hypothesized clinical advantages of biodegradable polymer DES over the medium- to long-term.

Future perspective

The most important question that remains to be answered is whether the promise inherent in biodegradable DES technology will be translated into improved long-term patient outcomes. It is hoped that 3–5-year follow-up of patients

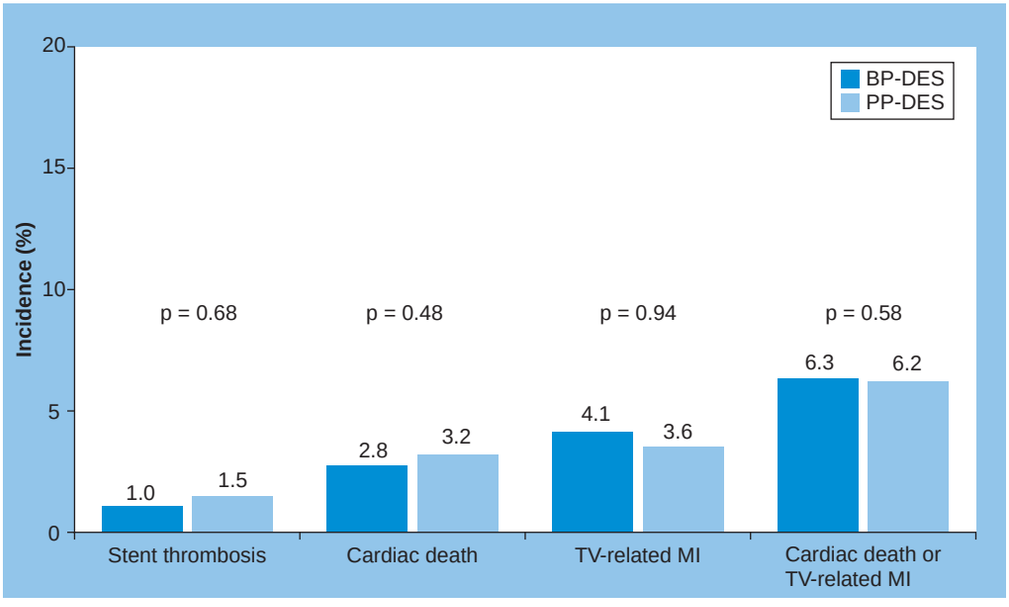

Figure 2. Device safety at 1 year. Incidence of cardiac death, myocardial infarction related to the target vessel and definite/probable stent thrombosis for biodegradable polymer and permanent polymer DES.
BP-DES: Biodegradable polymer drug-eluting stent; MI: Myocardial infarction; PP-DES: Permanent polymer drug-eluting stent; TV: Target vessel.

from large-scale clinical trials – including ISAR-TEST-3 [15], LEADERS [21] and ISAR-TEST-4 [16] – will shed some definitive light on this issue. In this respect, the use of the sirolimus-eluting Cypher and everolimus-eluting Xience-V as comparator stents in these studies is important as they may be thought to represent the current gold standard in permanent polymer DES devices. Any signal of improved late safety outcomes with biodegradable polymer DES may also have significant implications in terms of potential for reducing the duration of dual antiplatelet therapy after stenting and mitigation of associated patient morbidity and economic costs.

In the meantime, preliminary data from smaller studies examining surrogates of arterial healing after biodegradable DES implantation show somewhat conflicting results. On the one hand, systematic angiographic follow-up of the ISAR-TEST-3 after 2 years demonstrate that ongoing 'late luminal creep' between 6 and 8 months and 2 years (something specific to DES as opposed to bare-metal stent therapy) was observed with both biodegradable polymer sirolimus-eluting stent and permanent polymer sirolimus-eluting stent (Cypher) [27]. This may comprise indirect evidence that delayed neointimal formation and delayed arterial healing may not be eliminated by a switch to biodegradable DES. By way of explanation, it is possible that inflammatory response to monomer breakdown products is persistent [28]. However, while angiographic follow-up studies allow data to be collected on large numbers of patients, specific morphological information on vessel wall healing is not captured. In this respect the application of optical coherence tomography to the coronary arena is a very significant development [29]. First results of optical coherence tomography follow-up from a LEADERS substudy (n = 46) appear to show some signals of improved vascular healing with biodegradable polymer DES – fewer uncovered struts as compared with the Cypher stent against a background of a similar degree of mean late loss [30]. However, there remains some distance to be travelled before optical coherence tomography markers of vascular healing can be validated as surrogates of late clinical events. Finally, encouraging results have also been reported with DES utilizing, not only with a biodegradable polymer matrix, but also a bioresorbable stent backbone. These platforms have typically been constrained by necessity for thick stent struts and impaired radial strength, although recent iterations show promise in terms of overcoming these limitations [31].

Information resources

Further details of the trial along with a webcast from the European Society of Cardiology Hotline, presentation slides and comment from lead discussant Aaron Kugelmass, can be found at: www.escardio.org/congresses/esc-2009/congress-reports/Pages/707009–707010-mehilli-kugelmass.aspx

Executive summary

Stent platform

- The biodegradable polymer drug-eluting stent (DES) platform comprises a thin-strut, microporous and stainless steel backbone, which is coated on-site with a mixture of sirolimus, biodegradable polymer and shellac resin.
- Approximately 90% of the drug has been eluted by 28 days, with approximately 50% eluted over the course of the first 14 days.

Trial design

- ISAR-TEST-4 enrolled 2603 all-comer patients and assigned them to either biodegradable polymer sirolimus-eluting stent (n = 1299) or permanent polymer sirolimus-eluting (Cypher; n = 652) or everolimus-eluting (Xience-V; n = 652) stents.
- The trial utilized a hard clinical primary end point: a device-orientated composite of cardiac death, myocardial infarction related to the target vessel and revascularization of the target lesion.
- Use of the Cypher and Xience-V DES as comparator stents is noteworthy as these may represent the current gold standard in permanent polymer DES devices.

Clinical efficacy

- Biodegradable polymer DES was noninferior to permanent polymer DES concerning the incidence of the primary end point at 1 year (13.8 vs 14.4%, respectively; p-noninferiority = 0.005; relative risk: 0.96; 95% CI: 0.78–1.17; p-superiority = 0.66).
- Rates of target lesion revascularization were similar with both stents (8.8 vs 9.4%; p = 0.58).

Safety & tolerability

- Biodegradable polymer DES in comparison with permanent polymer DES showed similar 1-year rates of cardiac death or myocardial infarction related to the target vessel (6.3 vs 6.2%; p = 0.94) and stent thrombosis (definite/probable: 1.0 vs 1.5%; p = 0.29).

Future perspective

- Demonstration that a biodegradable polymer sirolimus-eluting stent is noninferior to permanent polymer-based DES, in terms of 1-year clinical efficacy, provides a framework for testing the potential clinical advantage of biodegradable polymer DES over the medium- to long-term.

Financial & competing interests disclosure

The microporous metal stent platform utilized in the biodegradable polymer drug-eluting stent is produced by Translumina, Hechingen, Germany who had no input into the study design, conduct or funding of ISAR-TEST-4. Adnan Kastrati reports submission of a patent application in respect of the biodegradable polymer coating technology. The biodegradable polymer drug-eluting stent is not commercially available and the authors receive no remuneration of any sort related to the stent platform.

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

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