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Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial‡

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Aims Although biodegradable polymer drug-eluting stent (DES) platforms have potential to enhance long-term clinical outcomes, data concerning their efficacy are limited to date. We previously demonstrated angiographic antirestenotic efficacy with a microporous, biodegradable polymer DES. In the current study, we hypothesized that at 12 months, its clinical safety and efficacy would be non-inferior to that of permanent polymer DES.

Methods and results This prospective, randomized, open-label, active-controlled trial was conducted at two tertiary referral cardiology centres in Munich, Germany. Patients presenting with stable coronary disease or acute coronary syndromes undergoing DES implantation in *de novo* native-vessel coronary lesions were randomly assigned to treatment with biodegradable polymer DES (rapamycin-eluting; $n = 1299$) or permanent polymer DES ($n = 1304$: rapamycin-eluting, Cypher, $n = 652$; or everolimus-eluting, Xience, $n = 652$) and underwent clinical follow-up to 1 year. The primary endpoint was a composite of cardiac death, myocardial infarction (MI) related to the target vessel, or revascularization related to the target lesion (TLR). Biodegradable polymer DES was non-inferior to permanent polymer DES concerning the primary endpoint [13.8 vs. 14.4%, respectively, $P_{\text{non-inferiority}}$ 0.005; relative risk = 0.96 (95% confidence interval, 0.78–1.17), $P_{\text{superiority}} = 0.66$]. Biodegradable polymer DES in comparison with permanent polymer DES showed similar rates of cardiac death or MI related to the target vessel (6.3 vs. 6.2%, $P = 0.94$), TLR (8.8 vs. 9.4%, $P = 0.58$), and stent thrombosis (definite/probable: 1.0 vs. 1.5%, $P = 0.29$). Subgroup analysis of the biodegradable polymer DES vs. individual Cypher and Xience stent arms revealed no signal of performance difference.

Conclusion A biodegradable polymer rapamycin-eluting stent is non-inferior to permanent polymer-based DES in terms of clinical efficacy over 1 year. These results provide a framework for testing the potential clinical advantage of biodegradable polymer DES over the medium to long term.
The trial was registered at ClinicalTrials.gov (identifier: NCT00598676).

Keywords Biodegradable • Coronary restenosis • Drug-eluting stents • Polymer • Rapamycin

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Introduction

In comparison with bare metal stenting, drug-eluting stent (DES) therapy effectively reduces restenosis across the spectrum of coronary disease presentations.[1] To date, permanent polymer coating has proven the most successful method to facilitate drug loading and release, key determinants of DES device efficacy in clinical practice.[2–5] An important limitation of such a non-erodible coating, however, is that it remains exposed to the coronary arterial milieu long after its useful function has been served. Indeed, a number of animal and human studies have implicated durable polymer residue as a cause of persistent arterial wall inflammation and delayed vascular healing.[6–9] This may play a significant role in the occurrence of stent thrombosis and restenosis late (>12 months) after intervention, events primarily reported in permanent polymer-based DES.[10–14]

The ISAR (individualizable drug-eluting stent system to abrogate restenosis) stent project seeks to investigate novel DES coatings, yielding a high antirestenotic efficacy without recourse to permanent polymer.[15–19] Previous experience revealed that although a completely polymer-free microporous DES platform effectively reduced restenosis, it was not non-inferior to currently available gold-standard DES platforms.[18]

Biodegradable polymer coatings offer the attractive prospect of superior control of drug delivery without the long-term sequelae of polymer residue.[20] Although DES platforms utilizing this technology have the potential to enhance long-term outcomes, published randomized control trial data demonstrating efficacy in significant patient numbers are limited to two studies: the ISAR-TEST-3 ($n = 605$) and LEADERS ($n = 1707$) trials.[18,21] In the current study, we sought to compare the efficacy of a rapamycin-eluting biodegradable polymer stent against the two leading FDA-approved permanent polymer-based DES platforms—the rapamycin-eluting Cypher stent and the everolimus-eluting Xience stent—in a trial powered for clinical events.

Methods

Study population, protocol, and device description

Patients older than age 18 with ischaemic symptoms or evidence of myocardial ischaemia (inducible or spontaneous) in the presence of ≥50% *de novo* stenosis located in native coronary vessels were considered eligible, provided that written informed consent by the patient or her/his legally authorized representative for participation in the study was obtained. Patients with a target lesion located in the left main stem, cardiogenic shock, malignancies, or other co-morbid conditions with life expectancy <12 months or that may result in protocol non-compliance, known allergy to the study medications (everolimus and rapamycin), or pregnancy (present, suspected, or planned) were considered ineligible for the study. Enrollment took place between September 2007 and August 2008. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. The trial protocol was approved by the institutional Ethics Committee responsible for the participating centres, Deutsches Herzzentrum and 1. Medizinische Klinik, Klinikum rechts der Isar, both in Munich, Germany.

In each participating centre, allocation to treatment was made by means of sealed, opaque envelopes containing a computer-generated sequence; randomization was performed immediately after decision to proceed with percutaneous coronary intervention (PCI). Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized in the order that they qualified. Randomization was stratified only according to participating centre. Patient allocation to each of the two treatment groups was in equal proportions. Both treatment groups were studied concurrently. Time 0 was defined as the time of randomization and patients were considered enrolled in the study at this time point. The same randomly assigned stent had to be implanted in all lesions in those patients who required stenting in multiple lesions and the use of more than one stent per lesion was also allowed. Patients were assigned to receive biodegradable polymer DES or permanent polymer DES [either rapamycin-eluting; Cypher (Cordis, Miami Lakes, FL, USA)] or everolimus-eluting; Xience (Abbott Vascular, Abbott Park, IL, USA)] in a 2 : 1 : 1 allocation.

The biodegradable polymer stent platform consists of a premounted, sand-blasted, 316L stainless steel microporous stent which is coated on site with a mixture of rapamycin, biodegradable polymer, and shellac resin (a biocompatible resin widely used in the coating of medical tablets). A detailed description for creating the micropores and its rationale, the specifics of the coating process, and the rapamycin release profile of the platform have been reported previously.[15,16,18,22] Description of stent platforms and elution characteristics of both permanent polymer stents are reported elsewhere.[23,24]

Study protocol

An oral loading dose of 600 mg clopidogrel was administered to all patients at least 2 h prior to the intervention, regardless of whether the patient was taking clopidogrel prior to admission. During the procedure, patients were given intravenous aspirin, heparin, or bivalirudin; glycoprotein IIb/IIIa inhibitor usage was at the discretion of the operators. After the intervention, all patients, irrespective of treatment allocation, were prescribed 200 mg/day aspirin indefinitely, clopidogrel 150 mg for the first 3 days (or until discharge) followed by 75 mg/day for at least 6 months, and other cardiac medications according to the judgement of patient's physician (e.g. beta-blockers, ACE-inhibitors, statins, etc.). After enrolment, patients remained in hospital for at least 48 h. Blood samples were drawn every 8 h for the first 24 h after randomization and daily afterwards for the determination of cardiac markers (CK, CK-MB and troponin T or I). Daily recording of ECG was also performed until discharge. All patients were evaluated at 1 and 12 months by phone or office visit. Repeat coronary angiography was scheduled for 6–8 months.

Data management, endpoints, and definitions

Relevant data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Centre. All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups. Baseline, post-procedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic (QCA) core laboratory (ISARESEARCH Center, Munich, Germany) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems) by two independent experienced operators unaware of the treatment allocation. Measurements were performed on cineangiograms recorded after the intracoronary administration of nitro-glycerine using the same single worst-view projection at all times. The contrast-filled non-tapered catheter tip was used for calibration.

Quantitative analysis was performed on both the 'in-stent' and 'in-segment' area (including the stented segment, as well as both 5 mm margins proximal and distal to the stent). Qualitative morphological lesion characteristics were characterized by standard criteria.

The primary endpoint of the study was a device-oriented composite of cardiac death, myocardial infarction (MI) related to the target vessel, or revascularization related to the target lesion (TLR) at 12 months post-index intervention.[25] Secondary endpoints were in-segment binary restenosis at follow-up angiography, in-stent late lumen loss (defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up angiography), all-cause mortality, and incidence of definite/probable stent thrombosis. Cardiac death is defined as death due to any of the following: acute MI; cardiac perforation/pericardial tamponade; arrhythmia or conduction abnormality; stroke within 30 days of the procedure or stroke suspected of being related to the procedure; death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery; or any death in which a cardiac cause cannot be excluded. Myocardial infarction related to procedure was defined as either an increase in CK-MB (or CK) $\geq$3 upper limit of normal (ULN) and at least 50% over the most recent pre-PCI levels, or the development of new ECG changes consistent with MI and CK-MB (CK) elevation higher than the ULN at two measurements for patients undergoing DES implantation in setting of stable angina pectoris or non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and falling or normal CK-MB (CK) levels. Recurrent chest pain lasting $>$30 min with either new ECG changes consistent with second MI or next CK-MB (CK) level at least 8–12 h after PCI elevated at least 50% above the previous level was considered procedure-related MI for patients presenting with NSTE-ACS and elevated CK-MB (CK) level prior to PCI. Bypass surgery-related MI was considered either CK-MB elevation $\geq$10 ULN and at least 50% over the most recent pre-surgery levels or CK-MB elevation $\geq$5 ULN and at least 50% over the most recent pre-surgery levels in addition to new abnormal Q-waves on the ECG. Spontaneous MI was defined as any CK-MB increase with or without the development of Q-waves on ECG. Target vessel revascularization was defined as any ischaemia-driven repeat PCI of the target lesion or bypass surgery of the target vessel. Ischaemia-driven was defined by: diameter stenosis $\geq$50% ('in-segment' QCA-analysis) at follow-up angiography and positive functional study corresponding to the area served by the target lesion or ischaemic symptoms and ECG-changes at rest referable to the target lesion; diameter stenosis $<$50% at follow-up angiography but a markedly positive functional study or ECG-changes corresponding to the territory supplied by target vessel; or diameter stenosis $\geq$70% at follow-up angiography in absence of documented clinical or functional ischaemia. Target vessel revascularization was defined as any ischaemia-driven repeat PCI or bypass surgery revascularization of any segment of the treated coronary vessel proximal or distal to the treated segment and including upstream and downstream side branch vessels. Stent thrombosis was classified according to the Academic Research Consortium (ARC) criteria.[25]

Statistical analysis

The objective of the study was to assess the non-inferiority of biodegradable polymer DES compared with permanent polymer DES. The null hypothesis regarding the primary endpoint was that the biodegradable polymer DES was inferior to the permanent polymer DES. The alternative hypothesis was that the biodegradable polymer DES was non-inferior to the permanent polymer DES. We 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 non-inferiority (Δ) of 3% would have 80% power to reject the null hypothesis in favour of the alternative hypothesis, assuming that the incidence of the primary endpoint in both groups was 10%. In order to account for possible loss to follow-up, we planned to enrol 1300 patients in each group. Sample size calculation was performed with nQuery Advisor (Statistical Solutions, Cork, Ireland) according to the method described by O'Brien and Muller.[26] After the determination of non-inferiority, we performed standard superiority testing including calculation of 95% confidence intervals (CIs) for relative risk with a two-tailed P-value $<$0.05 considered statistically significant. Relative risk was calculated using time-to-event analyses and compared using the log-rank test based on the Mantel–Haenszel method. The analysis of primary and secondary endpoints was planned to be performed on an intention-to-treat basis.[27] Although there are alternative opinions preferring a per protocol analysis in trials with a non-inferiority design, in view of the absence of cross-over, this issue is of no relevance to the current study. The non-inferiority hypothesis was tested with EquivTest (Statistical Solutions) according to the methods described by Hauck and Anderson.[28]

Continuous data are presented as mean (SD) or median (25th–75th percentiles). Categorical data are presented as counts or proportions (%). Unless otherwise stated, differences between groups were checked for significance using Student's t-test (continuous data) and χ^2 or Fisher's exact test where the expected cell value was $<$5 (categorical variables). Survival was assessed using the methods of Kaplan–Meier.

Pre-specified analysis consisted of paired comparisons of biodegradable polymer DES with permanent polymer rapamycin-eluting stents and with permanent polymer everolimus-eluting stents regarding primary and secondary endpoints. Additional pre-specified subsets of interest were old and young patients, men and women, diabetic and non-diabetic patients, and small and large vessels. To identify whether there was an interaction between treatment effect and these covariates, we used a Cox proportional hazards model.

Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp., Seattle, WA, USA) was used for analysis.

Results

In total, 2603 patients were enrolled and randomized to receive biodegradable polymer DES (n = 1299) or permanent polymer DES (n = 1304: Cypher, n = 652; Xience, n = 652). The groups were well matched in terms of baseline patient characteristics as shown in *Table 1*. The number of treated lesions was 3372 (biodegradable polymer DES, n = 1689; permanent polymer DES, n = 1683). More than one lesion was treated in 28.9% of patients in the biodegradable polymer group vs. 26.1% in the permanent polymer group (P = 0.11). Baseline lesion and procedural characteristics were also similar between the two groups (*Table 2*). Maximum troponin levels post-procedure were similar between both groups (biodegradable polymer DES 0.7 $\pm$ 2.8 μg/L vs. permanent polymer DES 0.7 $\pm$ 2.5 μg/L, P = 0.96).

There were no significant differences between the groups regarding clinical outcomes at 30 days (*Table 3*). The composite of cardiac death or MI related to the target vessel occurred at a rate of 4.4% with the biodegradable polymer DES vs. 4.5% with the permanent polymer DES (P = 0.87). There were five cases (0.4%) of definite stent thrombosis in each group (P = 0.81).

One-year follow-up was complete on all but 80 patients (3.1%). In these patients, median duration of follow-up was 5.7 (0.3–7.2)

Table 1 Baseline patient characteristics

	Biodegradable polymer DES, $n = 1299$	Permanent polymer DES, $n = 1304$	*P*-value
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
Hypertension	897 (69.1)	881 (67.6)	0.41
Hyperlipidaemia	868 (66.8)	846 (64.9)	0.30
Current smoker	202 (15.6)	215 (16.5)	0.52
Prior myocardial infarction	372 (28.6)	373 (28.6)	0.99
Prior bypass surgery	129 (9.9)	129 (9.9)	0.97
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
Ejection fraction[a]	53.1 ± 11.9	53.6 ± 11.3	0.34

Data shown as means ± SD or number (percentage). DES, drug-eluting stent.
[a]Data available for 2272 patients (87.3%).

Table 2 Angiographic and procedural characteristics

	Biodegradable polymer DES, $n = 1683$	Permanent polymer DES, $n = 1689$	*P*-value
Target vessel			0.93
Left anterior descending	753 (44.7)	748 (44.3)	
Left circumflex	454 (27.0)	453 (26.8)	
Right coronary artery	476 (28.3)	488 (28.9)	
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
Minimal lumen diameter, pre	0.98 ± 0.50	0.98 ± 0.51	0.97
Balloon diameter	3.10 ± 0.49	3.10 ± 0.52	0.99
Balloon pressure, max	15.5 ± 3.2	15.5 ± 3.1	0.68
Minimal lumen diameter, post	2.58 ± 0.44	2.59 ± 0.50	0.40

Data shown as means ± SD or number (percentage). DES, drug-eluting stent.

months. In accordance with the study protocol, follow-up angiography at 6–8 months was performed in 78% of patients.

The results of 1-year follow-up are shown in *Table 4*. Regarding the primary endpoint of cardiac death/MI related to target vessel/TLR, the biodegradable polymer DES was non-inferior to permanent polymer DES [13.8 vs. 14.4%, respectively, $P_{\text{non-inferiority}}$ 0.005; relative risk = 0.96 (95% CI, 0.78–1.17), $P_{\text{superiority}} = 0.66$]. *Figure 1* shows survival analysis curves for freedom from occurrence of the primary endpoint.

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), $P = 0.94$], and TLR (8.8 vs. 9.4%, respectively; relative risk = 0.93 (95% CI, 0.72–1.21), $P = 0.58$].

The rate of ARC definite/probable stent thrombosis was also similar between the biodegradable polymer DES and the permanent polymer DES groups [1.0 vs. 1.5%, respectively; relative

Table 3 Clinical results at 30 days

	Biodegradable polymer DES, $n = 1299$	Permanent polymer DES, $n = 1304$	*P*-value
Cardiac death	12 (0.9)	18 (1.4)	0.28
MI related to target vessel	45 (3.5)	40 (3.1)	0.57
Cardiac death or MI related to target vessel	55 (4.2)	56 (4.3)	0.94
Target lesion revascularization	7 (0.5)	8 (0.6)	0.80
Cardiac death, MI related to target vessel, or target lesion revascularization	57 (4.4)	59 (4.5)	0.87

Data shown as number (percentage). DES, drug-eluting stent; MI, myocardial infarction.

Table 4 Clinical results at 1 year

	Biodegradable polymer DES, $n = 1299$	Permanent polymer DES, $n = 1304$	Relative risk (95% CI)	*P*-value
Cardiac death	35 (2.8)	41 (3.2)	0.85 (0.54–1.33)	0.48
MI related to target vessel	53 (4.1)	46 (3.6)	1.16 (0.78–1.71)	0.48
Cardiac death or MI related to target vessel	81 (6.3)	80 (6.2)	1.01 (0.74–1.38)	0.94
Target lesion revascularization	109 (8.8)	116 (9.4)	0.93 (0.72–1.21)	0.58
Cardiac death, MI related to target vessel, or target lesion revascularization	176 (13.8)	183 (14.4)	0.96 (0.78–1.17)	0.66
All-cause death	60 (4.7)	61 (4.8)	0.98 (0.69–1.40)	0.90
All myocardial infarction	55 (4.3)	53 (4.1)	1.04 (0.71–1.52)	0.84
Target vessel revascularization	170 (13.7)	172 (13.9)	0.98 (0.79–1.21)	0.83
Non-target vessel revascularization	114 (9.1)	109 (8.8)	1.03 (0.79–1.34)	0.81

Data shown as number (percentage by Kaplan–Meier analysis); risk ratios and *P*-values were calculated from superiority testing with the log-rank test. DES, drug-eluting stent; MI, myocardial infarction.

risk = 0.68 (95% CI, 0.34–1.38), $P = 0.29$; *Figure 2*]. Full results of stent thrombosis adjudication are shown in *Table 5*.

Comparison of the biodegradable polymer DES group vs. the individual component subgroups of the permanent polymer DES group revealed no signal of performance difference: rate of cardiac death/MI related to target vessel/TLR with biodegradable polymer DES 13.8% vs. Cypher 15.2% [relative risk = 0.90 (95% CI, 0.71–1.16), $P = 0.43$] and vs. Xience 13.6% [relative risk = 1.01 (95% CI, 0.78–1.31), $P = 0.94$].

In addition, comparison of outcomes for biodegradable polymer DES vs. permanent polymer DES in relation to the primary endpoint was not different according to analysis for each of the prespecified subgroups of age, sex, diabetes, and vessel size (*Figure 3*).

Discussion

In this prospective, randomized, assessor-blinded trial, we found that a biodegradable polymer rapamycin-eluting stent was not inferior to permanent polymer DES in a large-scale study powered for a composite clinical safety and efficacy endpoint. Furthermore, at 1 year, there was no signal of difference between biodegradable polymer DES and permanent polymer DES regarding individual efficacy (TLR) or safety (cardiac death/MI or stent thrombosis) endpoint components.

These findings are of some relevance in light of the ongoing debate relating to adverse events after DES implantation and the perceived culpability of permanent polymer in the pathophysiology of these events.[6–9] It should be acknowledged that, in general, concerns regarding a possible excess of stent thrombosis following DES implantation have not been borne out by extensive clinical follow-up of large numbers of treated patients.[29–31] Nonetheless, evidence does suggest that there is a temporal redistribution of post-stenting events, with some excess of stent thrombosis and restenosis with DES when compared with bare metal stents, beyond the 12-month time window.[10–13,32]

At present, the focus of DES development is towards devices which can optimize drug-release kinetics without recourse to permanent polymer. The rationale behind the employment of biodegradable polymer coating on a metal stent backbone is intuitively attractive: loading and elution of the lipophilic active-drug is facilitated by a biocompatible polymer, which after completion of its useful function is slowly degraded to inert organic monomers, thereby eliminating the risk associated with the long-term presence of polymer in the coronary vessel wall.[20] In addition, although fully biodegradable stent-and-polymer platforms have shown

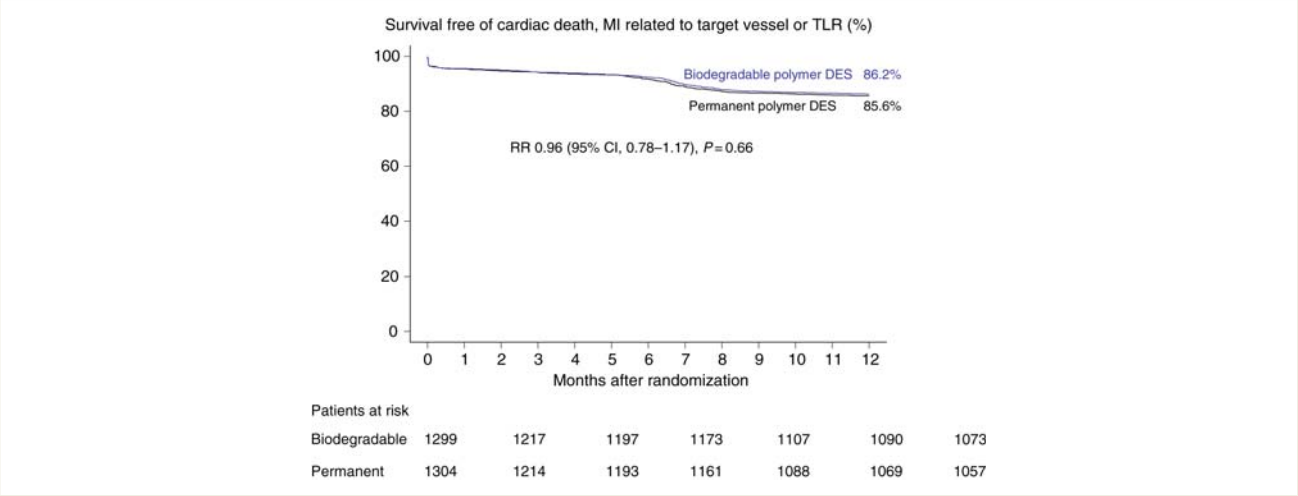

Figure 1 Survival curve for freedom from the primary endpoint of cardiac death, myocardial infarction (MI) related to the target vessel (TLR) or revascularization related to the target lesion (TLR) for biodegradable polymer and permanent polymer drug-eluting stents. CI, confidence interval; DES, drug-eluting stent; RR, relative risk. *P*-values are two-sided from superiority testing (log-rank test).

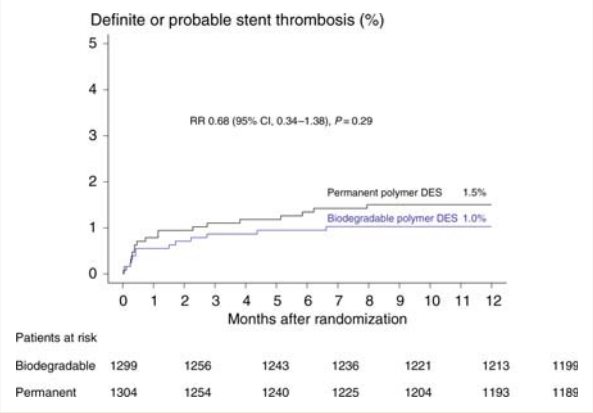

Figure 2 Time to event curve for definite/probable stent thrombosis according to Academic Research Consortium criteria for biodegradable polymer and permanent polymer drug-eluting stent. CI, confidence interval; DES, drug-eluting stent; RR, relative risk. *P*-value are two-sided from superiority testing (log-rank test).

encouraging results,[33] the presence of an underlying metal alloy backbone appears to offer superior mechanical support and enhanced antirestenotic efficacy. The promise inherent in this model has prompted a number of studies with novel biodegradable polymer platforms in the recent past.[18,21,34–37] In particular, the LEADERS investigators have shown non-inferiority against the permanent polymer Cypher DES with a biolimus-eluting biodegradable polymer DES in a trial which similar to the current study was powered for clinical endpoints.[21]

To date, however, the clinical advantage of biodegradable polymer remains presumptive. In an earlier clinical trial, we demonstrated high antirestenotic efficacy with the same biodegradable polymer DES (non-inferior to that of the Cypher stent) in an angiographic endpoint trial.[18] Subsequently, although we extended follow-up out to 2 years, there was no signal of a safety advantage with this novel platform, although the number of patients enrolled would make demonstration of a true difference unlikely.[38] In this respect, it is to be hoped that both the current ISAR-TEST-4 trial and the LEADERS trial will provide a sound basis for testing the hypothesized safety advantage of biodegradable polymer DES and in time to come they will provide a definitive answer to this question by means of extended clinical follow-up of large patient numbers.

A second caveat regarding late clinical performance of biodegradable polymer DES should also be mentioned. The premise behind biodegradable polymer technology is that after the polymer is degraded (at a variable time point post-implantation dependent on the specifics of polymer composition), it is expected that late antirestenotic performance would resemble that of a polymer-free DES or a bare metal stent—i.e. no further late loss beyond 6–8 months or even a small increase in luminal calibre due to late neointimal contraction.[13,39,40] However, this may not invariably hold true. In particular, although bench testing of our device suggests that biodegradable polymer is completely degraded at 6–9 weeks, serial angiographic follow-up of our ISAR-TEST-3 sample out to 2 years demonstrated a small degree of delayed late loss ('late luminal creep') between 6–8 months and 2 years with the biodegradable polymer DES.[38] One possible explanation is that inflammatory reaction associated with biodegradable polymer breakdown can be significant and that immune response to monomer breakdown products may sometimes be biologically persistent.[41] These findings further emphasize the importance of long-term clinical follow-up following DES implantation.

Strengths and limitations of this study

The population enrolled in the ISAR-TEST-4 trial is relatively non-selected, comprising patients presenting with stable coronary

Table 5 Stent thrombosis at 1 year according to Academic Research Consortium criteria

	Biodegradable polymer DES, $n = 1299$	Permanent polymer DES, $n = 1304$	Relative risk (95% CI)	*P*-value
Definite	8 (0.6)	12 (1.0)	0.67 (0.27–1.62)	0.37
Probable	5 (0.4)	7 (0.6)	0.71 (0.23–2.23)	0.56
Possible	6 (0.5)	7 (0.6)	0.85 (0.29–2.53)	0.77
Definite or probable	13 (1.0)	19 (1.5)	0.68 (0.34–1.38)	0.29

Data shown as number (percentage by Kaplan-Meier analysis); risk ratios and *P*-values were calculated from superiority testing with the log-rank test. DES, drug-eluting stent.

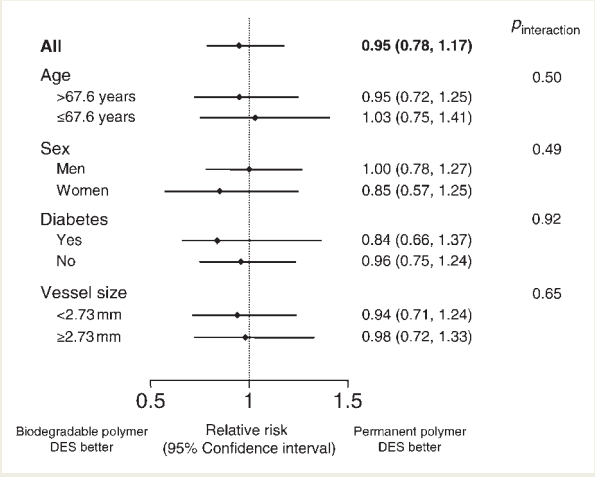

Figure 3 Comparison of biodegradable polymer or permanent polymer drug-eluting stent in pre-specified subgroups regarding the primary composite endpoint. Cut-off values for age and vessel size are those defining the median value for the entire population. DES, drug-eluting stent.

disease or ACS, reflecting routine clinical practice at the enrolling institutions where the overwhelming majority of patients consent to participation in randomized clinical trials. A high proportion of patients had diagnosed diabetes mellitus, history of prior infarction, and documented multivessel coronary disease. Lesion complexity was also typical for real-world practice. These observations increase the likelihood that findings may be generalizable to day-to-day clinical care. In addition, the choice of comparator permanent polymer stents is noteworthy, as both Cypher and Xience may be thought to represent the current gold standard in DES technology.

In terms of limitations, patients with in-stent restenosis, left main stem disease, and index lesion in a bypass graft were not represented in this study. Furthermore, logistical constraints prevent blinding of the operators to stent type at implantation. Against this, however, all assessments, be they clinical or angiographic, were performed in a blinded manner. Additionally, the influence of angiographic follow-up on the individual components of the primary endpoint should be considered. This may increase the incidence of TLR in a manner that may not reflect routine clinical practice, although the relative magnitude of an observed treatment effect may be expected to be real. Finally, at the 1-year time point of assessment, differences between the platforms particularly with regard to safety events might not necessarily be expected. Nonetheless, as discussed previously, this trial provides a sound basis to test for outcome differences between biodegradable and permanent polymer DES by means of extended follow-up of this large study sample over the medium to long term.

Conclusion

In the ISAR-TEST-4 trial, we have demonstrated that a biodegradable polymer DES is non-inferior to two leading permanent polymer-based DES in a large-scale study powered for hard clinical endpoints. Although, in general terms, the promise of biodegradable polymer technology remains to be fully realized, the current study represents a framework in which the potential safety and efficacy advantages of biodegradable polymer DES platforms may be tested over the years to come.

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Conflict of interest: The microporous metal stent platform utilized in the biodegradable polymer DES is produced by Translumina, Hechingen, Germany, who had no input into the study design, conduct, or funding. A.S. and A.K. report submission of a patent application in respect of the biodegradable polymer coating technology. The biodegradable polymer DES is not commercially available and none of the authors receive remuneration of any sort related to the stent platform. A.K. reports having received lecture fees from Cordis and Medtronic; J.M. reports having received lecture fees from Cordis. No other conflicts of interest are declared.

Appendix

Study organization

Steering committee: A.S. (Chairman), A.K. (Principal Investigator), and J.M. *Participating centres*: Deutsches Herzzentrum, Technische Universität, Munich, Germany, and 1. Medizinische Klinik, Klinikum

rechts der Isar, Technische Universität, Munich, Germany. *Data Safety Monitoring Board*: J. Mann (Chairman), F. Hoffmann, and K. Ulm (biostatistician). *Clinical Event Adjudication Committee*: D. Hall† (Chairman), G. Ndrepepa, and D. Poci. *Data Coordination*: ISARESEARCH Centre: J.M. (Director), K.A.B., M. Dirlewanger, B. Gließl, H. Holle, S.K., K. Hösl, N. Rifatov, F. Maimer-Rodrigues, N. Sargon, and S.S. *Angiographic Core Laboratory*: ISARESEARCH Centre: A. Bergbauer, O. Bruskina, R.A.B., S. Hurt, R. Iijima, S. Pinieck, and S. Ranfl.

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