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Biodegradable Polymer Versus Permanent Polymer Drug-Eluting Stents and Everolimus- Versus Sirolimus-Eluting Stents in Patients With Coronary Artery Disease

3-Year Outcomes From a Randomized Clinical Trial

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Objectives The aim of this study was to compare the 3-year efficacy and safety of biodegradable polymer with permanent polymer stents and of everolimus-eluting stents (EES) with sirolimus-eluting stents (SES).

Background Biodegradable polymer drug-eluting stents (DES) offer potential for enhanced late outcomes in comparison with permanent polymer stents. In addition, there is increasing interest in the comparison of EES (Xience, Abbott Vascular, Abbott Park, Illinois) versus SES (Cypher, Cordis Corporation, Miami Lakes, Florida).

Methods The ISAR-TEST 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents-4) was a randomized clinical trial with broad inclusion criteria, enrolling 2,603 patients at 2 clinics in Munich, Germany. Patients were randomized to either biodegradable polymer (n = 1,299) or permanent polymer stents (n = 1,304); patients treated with permanent polymer stents were randomly allocated to EES (n = 652) or SES (n = 652). The primary endpoint was the composite of cardiac death, target vessel-related myocardial infarction, or target lesion revascularization.

Results Clinical events continued to accrue at a low rate out to 3 years in all groups. Overall, there was no significant difference between biodegradable polymer and permanent polymer DES with regard to the primary endpoint (20.1% vs. 20.9%, hazard ratio [HR]: 0.95, 95% confidence interval [CI]: 0.80 to 1.13; p = 0.59). Rates of definite/probable stent thrombosis were also similar in both groups (1.2% vs. 1.7%, respectively; HR: 0.71, 95% CI: 0.37 to 1.39; p = 0.32). In patients treated with permanent polymer stents, EES were comparable to SES with regard to the primary endpoint (19.6% vs. 22.2%, respectively; HR: 0.87, 95% CI: 0.68 to 1.11; p = 0.26) as well as definite/probable stent thrombosis (1.4% vs. 1.9%, HR: 0.75, 95% CI: 0.32 to 1.78; p = 0.51).

Conclusions Biodegradable polymer and permanent polymer DES are associated with similar clinical outcomes at 3 years. In addition, EES are comparable to SES in terms of overall clinical efficacy and safety. (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting STents [ISAR-TEST 4]: Prospective, Randomized Trial of 3-limus Agent-eluting Stents With Different Polymer Coatings; NCT00598676) (J Am Coll Cardiol 2011;58:1325–31)

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Abbreviations and Acronyms

CI = confidence interval
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization

Although first-generation drug-eluting stents (DES) are highly effective at preventing coronary restenosis, there is a collateral cost to be borne in terms of delayed healing of the stented arterial segment (1–3). Therefore, the motivation behind the development of newer devices has been the attainment of optimal antirestenotic efficacy at a minimum of arterial wall toxicity (4).

Biodegradable polymer DES offer controlled elution of active-drug from the stent backbone by means of a biocompatible polymer coating, which after completion of its useful function, slowly degrades to inert organic monomers, thereby dissipating the risk associated with the long-term presence of durable polymer in the coronary vessel wall. To date, 2 large-scale studies have demonstrated noninferiority of biodegradable polymer DES against standard-bearer permanent polymer DES at 1 year (5,6), but longer-term data with this therapy remain scant.

In terms of permanent polymer DES, the everolimus-eluting stent (EES) (Xience, Abbott Vascular, Abbott Park, Illinois) represents a potential step forward in stent technology. It has proven superior to the first-generation paclitaxel-eluting stent (Taxus, Boston Scientific, Natick, Massachusetts) in a number of randomized controlled studies (7,8), although benchmark evaluation against the standard-bearer first-generation sirolimus-eluting stent (SES) (Cypher, Cordis Corporation, Miami Lakes, Florida) in broadly inclusive lesion and patient subtypes remains a scientific gap.

We sought to address these outstanding issues by comparing the clinical efficacy and safety of biodegradable polymer stents with permanent polymer stents and of EES with SES at 3-year follow-up in the setting of the ISAR-TEST 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents-4) trial.

Methods

The ISAR-TEST 4 trial was an investigator-initiated, industry-independent, real-world randomized trial with broad inclusion criteria. The primary study comparison was between outcomes of patients treated with biodegradable polymer versus permanent polymer DES. The secondary study comparison was between outcomes of patients treated with EES versus SES. Details of the study population, methods, endpoints, and primary analysis have been previously reported (6).

Patients were assigned to receive biodegradable polymer (SES [stent backbone produced by Translumina, Hechingen, Germany]) or permanent polymer DES (either EES, Xience [Abbott Vascular], or SES, Cypher [Cordis Corporation]) in a 2:1:1 allocation. Full description of the biodegradable polymer stent platform has been reported previously (6).

The primary outcome of the ISAR-TEST 4 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).

Follow-up and analysis. Patients were evaluated at 1, 12, 24, and 36 months by telephone call or office visit. Repeat coronary angiography was scheduled for 6 to 8 months, and in those patients undergoing angiographic surveillance at this time point and not requiring TLR, a second angiographic follow-up was planned for 2 years. All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups. Details relating to statistical analyses are presented in the Online Appendix.

Results

A total of 2,603 patients were randomized to receive biodegradable polymer (n = 1,299) or permanent polymer (n = 1,304) DES (Fig. 1). Baseline patient and lesion characteristics according to randomization to biodegradable polymer or permanent polymer DES were well balanced in both groups, as previously reported, and shown in Online Table 1.

Patients allocated to treatment with permanent polymer DES were randomized to either EES (Xience, n = 652) or SES (Cypher, n = 652) (Fig. 1). Baseline patient and lesion characteristics according to randomization to EES or SES are shown in Table 1.

Biodegradable polymer versus permanent polymer DES: 3-year clinical follow-up. The results of follow-up are summarized in Table 2. At 3 years, the incidence of the primary composite endpoint of cardiac death/MI related to target vessel/TLR was not significantly different between biodegrad-

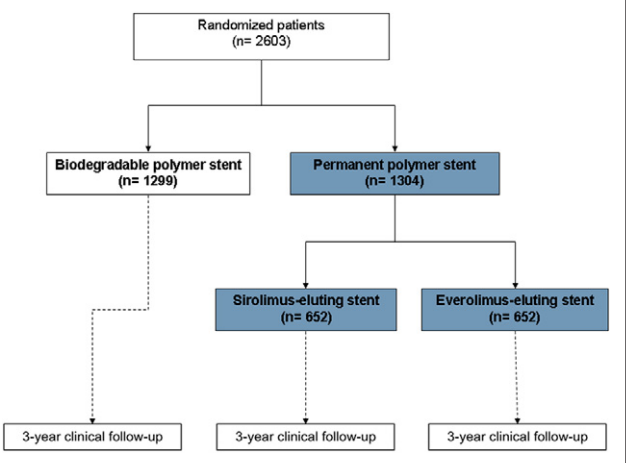

Figure 1 The ISAR-TEST 4 Study Flow Chart

Participant flow through the study.

Table 1 EES Versus SES: Characteristics of Patients and Lesions at Baseline

	EES	SES	p Value
Patients	n = 652	n = 652	
Age, yrs	66.7 ± 10.3	66.8 ± 11.1	0.93
Male	507 (77.8)	495 (75.9)	0.43
Diabetes mellitus	184 (28.2)	193 (29.6)	0.58
Insulin-dependent	60 (9.2)	62 (9.5)	0.85
Arterial hypertension	442 (67.8)	439 (67.3)	0.86
Hyperlipidemia	423 (64.9)	423 (64.6)	>0.99
Current smoker	101 (15.5)	114 (17.5)	0.33
Prior myocardial infarction	191 (29.3)	182 (27.9)	0.58
Prior coronary artery bypass grafting	69 (10.6)	60 (9.2)	0.40
Clinical presentation			0.49
Acute myocardial infarction	70 (10.7)	70 (10.7)	
Unstable angina	199 (30.6)	180 (27.6)	
Stable angina	383 (58.7)	402 (61.7)	
Ejection fraction, %*	53.4 ± 11.7	53.8 ± 12.1	0.64
Multilesion intervention	174 (26.7)	166 (25.5)	0.61
Multivessel disease	557 (85.4)	569 (87.3)	0.33
Lesions	n = 850	n = 839	
Target vessel location			0.59
Left anterior descending artery	372 (43.8)	376 (44.8)	
Left circumflex artery	223 (26.2)	230 (27.4)	
Right coronary artery	255 (30.0)	233 (27.8)	
Chronic total occlusion	36 (4.2)	50 (6.0)	0.11
Bifurcation	185 (21.8)	198 (23.6)	0.37
Ostial	158 (18.6)	146 (17.4)	0.53
Complex morphology (B2/C)	604 (71.1)	614 (73.2)	0.33
Lesion length, mm	15.2 ± 8.9	14.8 ± 8.2	0.37
Vessel size, mm	2.80 ± 0.45	2.80 ± 0.48	0.82
Minimum lumen diameter, mm			
Before procedure	0.99 ± 0.49	0.97 ± 0.51	0.48
After procedure	2.59 ± 0.45	2.59 ± 0.44	0.94
Percent stenosis, %			
Before procedure	64.8 ± 16.0	65.4 ± 16.1	0.51
After procedure, in-stent	11.8 ± 6.3	10.8 ± 6.2	<0.001
After procedure, in-segment	23.6 ± 11.4	23.3 ± 10.8	0.64

Values are mean ± SD or n (%). *Data available for 1,149 patients (88.1%).
EES = everolimus-eluting stent(s); SES = sirolimus-eluting stent(s).

able polymer and permanent polymer DES (20.1% vs. 20.9% respectively, hazard ratio [HR]: 0.95, 95% confidence interval [CI]: 0.80 to 1.13; p = 0.59) (Fig. 2A). The comparability between the 2 study devices with regard to the primary endpoint was observed across all pre-specified subgroups (Online Fig. 1).

In terms of antirestenotic efficacy, TLR at 3 years was also similar in both groups (Fig. 2B). With regard to safety outcomes, the incidence of adverse events between 1 and 3 years was low across the treatment groups. The composite of cardiac death/MI related to the target vessel was similar (Fig. 2C), and the rate of definite/probable stent thrombosis was low in both groups: 1.2% with biodegradable polymer DES versus 1.7% with permanent polymer DES (HR: 0.71, 95% CI: 0.37 to 1.39; p = 0.32) (Fig. 2D). Full results of stent thrombosis adjudication are presented in Table 2.

Everolimus-eluting versus SES: 3-year clinical follow-up. The results of follow-up are summarized in Table 3. The incidence of the primary composite endpoint of cardiac death/MI related to target vessel/TLR was not significantly different between EES and SES (19.6% vs. 22.3%, respectively; HR: 0.87, 95% CI: 0.68 to 1.11; p = 0.26) (Fig. 3A). The comparability between the 2 study devices with regard to the primary endpoint was observed across all pre-specified subgroups (Online Fig. 2).

In terms of antirestenotic efficacy, there was a numerically lower rate of TLR at 3 years with EES versus SES, although this was not statistically significant (Fig. 3B). With regard to safety outcomes, the composite of cardiac death/MI related to the target vessel was similar in both groups (Fig. 3C). The rate of definite/probable stent thrombosis at 3 years was 1.4% with EES versus 1.9%

Table 2 Biodegradable Polymer Versus Permanent Polymer Drug-Eluting Stents: Clinical Outcomes Out to 3 Years

	Biodegradable Polymer Stents (n = 1,299)	Permanent Polymer Stents (n = 1,304)	HR (95% CI)	p Value
All-cause death	117 (9.3)	123 (9.8)	0.95 (0.74–1.23)	0.71
Cardiac death	58 (4.7)	65 (5.2)	0.89 (0.63–1.27)	0.53
Target vessel myocardial infarction	59 (4.6)	56 (4.4)	1.06 (0.73–1.52)	0.77
Cardiac death or target vessel myocardial infarction	107 (8.5)	112 (8.9)	0.96 (0.73–1.25)	0.75
TLR	168 (13.9)	172 (14.2)	0.97 (0.78–1.20)	0.79
Primary endpoint*	252 (20.1)	263 (20.9)	0.95 (0.80–1.13)	0.59
Stent thrombosis				
Definite	9 (0.7)	13 (1.0)	0.69 (0.30–1.62)	0.39
Probable	6 (0.5)	8 (0.6)	0.75 (0.26–2.16)	0.59
Possible	12 (1.0)	15 (1.2)	0.80 (0.38–1.71)	0.57
Definite or probable	15 (1.2)	21 (1.7)	0.71 (0.37–1.39)	0.32

Values are n (percentage as Kaplan-Meier estimate). *Primary endpoint = composite of cardiac death, target vessel myocardial infarction, or target lesion revascularization (TLR).
CI = confidence interval; HR = hazard ratio.

with SES (relative risk: 0.75, 95% CI: 0.32 to 1.78; p = 0.51) (Fig. 3D). Full results of stent thrombosis adjudication are presented in Table 3.

Additional analyses. Results relating to patient-oriented outcomes did not differ across the groups and are presented in the Online Appendix. Landmark analyses at

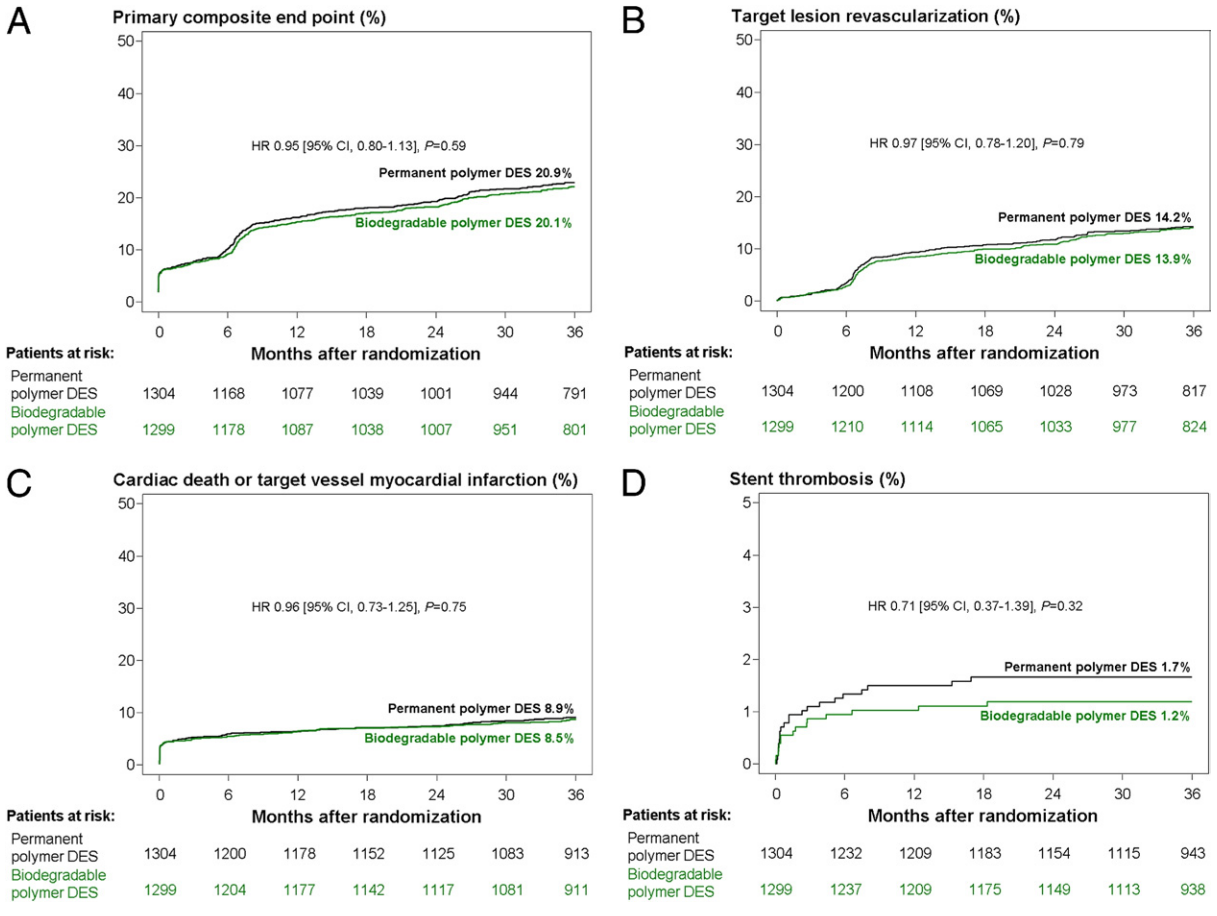

Figure 2 Comparison of Outcomes in Patients Treated With Biodegradable Polymer Versus Permanent Polymer DES

Kaplan-Meier curves for **(A)** primary endpoint (composite of cardiac death, target vessel myocardial infarction, or target lesion revascularization), **(B)** target lesion revascularization, **(C)** all-cause death, and **(D)** definite/probable stent thrombosis. CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio.

Table 3 EES Versus SES: Clinical Outcomes Out to 3 Years

	EES (n = 652)	SES (n = 652)	HR (95% CI)	p Value
All-cause death	58 (9.3)	65 (10.3)	0.90 (0.63–1.29)	0.57
Cardiac death	31 (5.0)	34 (5.4)	0.92 (0.56–1.49)	0.73
Target vessel myocardial infarction	26 (4.1)	30 (4.7)	0.87 (0.51–1.47)	0.60
Cardiac death or target vessel myocardial infarction	55 (8.7)	57 (9.0)	0.97 (0.67–1.41)	0.88
TLR	77 (12.8)	95 (15.5)	0.80 (0.59–1.08)	0.15
Primary endpoint*	123 (19.6)	140 (22.3)	0.87 (0.68–1.11)	0.26
Stent thrombosis				
Definite	4 (0.6)	9 (1.4)	0.44 (0.14–1.44)	0.16
Probable	5 (0.8)	3 (0.5)	1.67 (0.40–6.99)	0.48
Possible	5 (0.8)	10 (1.7)	0.50 (0.17–1.47)	0.20
Definite or probable	9 (1.4)	12 (1.9)	0.75 (0.32–1.78)	0.51

Values are n (percentage as Kaplan-Meier estimate). *Primary endpoint = composite of cardiac death, target vessel myocardial infarction, or TLR.
CI = confidence interval; HR = hazard ratio.

1 year are shown in Online Table 2. Quantitative coronary angiographic analysis results at 6 to 8 months and at 2 years for biodegradable polymer versus permanent polymer DES and EES versus SES are shown in the Online Appendix and detailed in Online Tables 3 and 4, respectively.

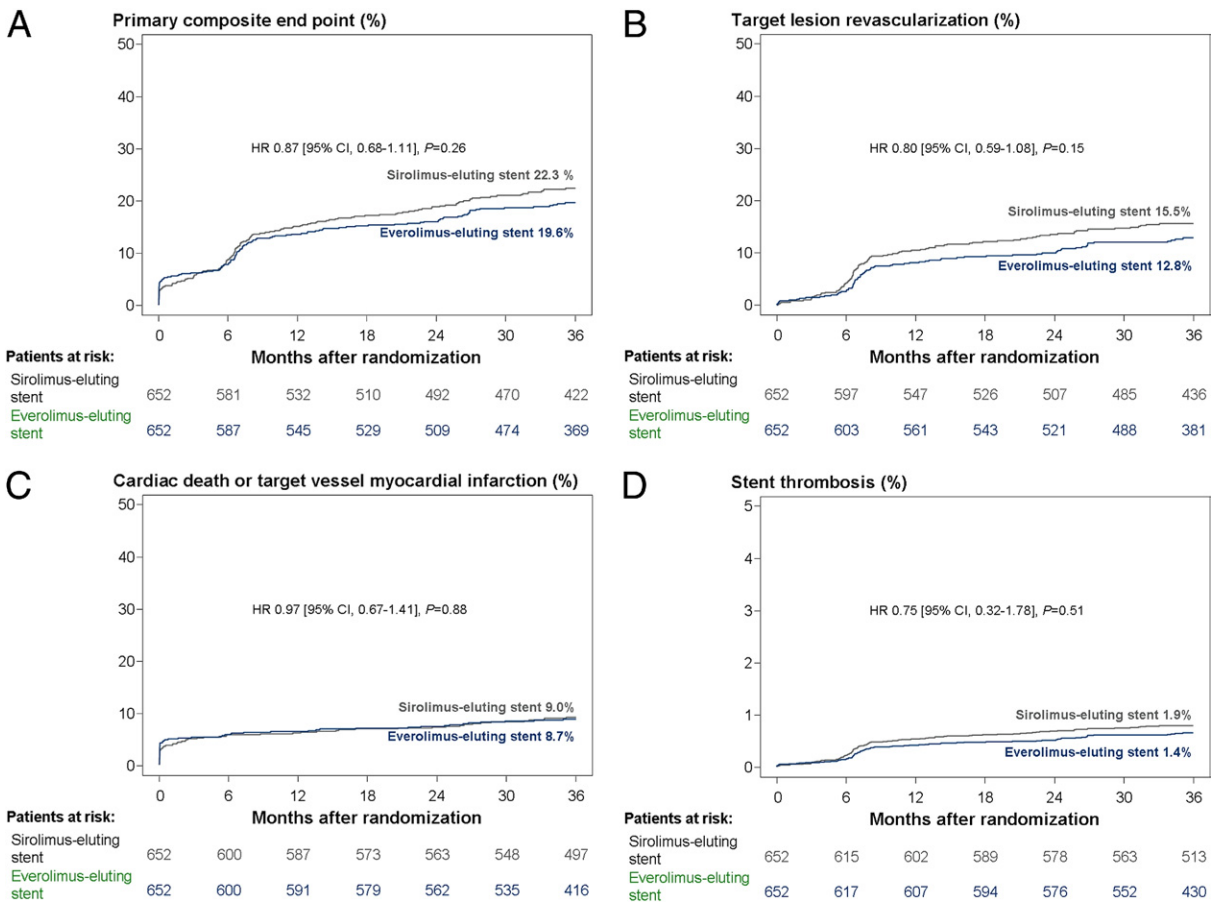

Figure 3 Comparison of Outcomes in Patients Treated With Everolimus-Eluting Versus Sirolimus-Eluting Stents

Kaplan-Meier curves for **(A)** primary endpoint (composite of cardiac death, target vessel myocardial infarction, or target lesion revascularization), **(B)** target lesion revascularization, **(C)** all-cause death, and **(D)** definite/probable stent thrombosis. Abbreviations as in Figure 2.

Discussion

The current paper reports the 3-year outcomes from a large-scale randomized trial with broad inclusion criteria, comparing outcomes of patients treated with biodegradable polymer versus permanent polymer DES and EES versus SES. The salient findings are: 1) biodegradable polymer and permanent polymer DES are associated with similar clinical outcomes at 3 years; 2) in patients treated with permanent polymer DES, EES stents are associated with similar clinical outcomes in comparison with SES; and 3) clinical events continued to accrue at a low rate out to 3 years, although rates of stent thrombosis were low across all treatment groups.

Biodegradable polymer versus permanent polymer DES. The present trial is the largest completed randomized trial involving patients treated with biodegradable polymer DES. The principal finding was that, in terms of clinical events, there was no significant difference in outcomes between patients treated with biodegradable polymer or permanent polymer DES. Notably, although a numerically lower rate of definite/probable stent thrombosis was observed with biodegradable polymer DES, this difference was not statistically significant, and the 95% CIs surrounding the risk reduction are broad and overlapping, reflecting the overall low incidence of events. This is an ongoing issue in trials of emerging DES technology, making the design of trials powered to detect safety benefit with comparator stents largely infeasible. In time, however, aggregate long-term data from completed or ongoing biodegradable polymer trials might conceivably shed some further light on this question.

EES versus SES. There is increasing interest in the comparison between the EES (Xience) and SES (Cypher). Although the EES has proven superior to the first-generation paclitaxel-eluting (Taxus) stent (7,8), it is well-recognized that this stent is a weak comparator (1). Indeed, benchmark evaluation against the SES Cypher in the setting of a randomized trial is imperative, before we can fully define the role of EES in contemporary practice.

The main finding of the ISAR-TEST 4 trial in this respect was that in a broadly inclusive patient cohort EES are associated with similar clinical outcomes in comparison with SES out to 3 years. These observations are in line with a recently published 2-year comparative analysis of both stents in large vessels (9) and also with the 9-month results from a second randomized trial (10). Furthermore, although there was no significant difference between the 2 stent platforms in terms of safety, the numerically lower rates of stent thrombosis observed with the EES seems to be a consistent feature of clinical trials with this stent. Moreover, the remarkably low incidence of definite stent thrombosis of 0.6% observed with EES at 3 years in the present study is in line with rates seen in other studies (7,8). Finally, in terms of antirestenotic performance, although there was no statistically significant difference in clinical efficacy, a trend was observed in favor of the everolimus-eluting stent in terms of both angiographic and clinical outcomes.

Strengths and limitations of ISAR-TEST 4. In terms of strengths, the present study is notable for its broad inclusion criteria. Furthermore, patient and lesion complexity was high, reflective of routine clinical practice at the enrolling institutions, where the overwhelming majority (>90%) of patients consent to participation in randomized clinical trials. Consequently, results are likely to be generalizable. Furthermore, the availability of outcome data out to 3 years permits capture of relatively late-occurring adverse safety and efficacy events.

In terms of limitations, the primary design of the ISAR-TEST 4 trial was a noninferiority comparison of biodegradable and permanent polymer DES at 12 months. Additional comparisons at 3 years should be regarded as post hoc. Furthermore, although comparison between EES and SES was pre-specified, the trial was not specifically powered for this comparison. In addition, the influence of angiographic follow-up on the individual components of the primary endpoint should be considered. Finally, although both treatment groups received the same recommendation for duration of treatment after stenting, complete data relating to actual duration of dual antiplatelet therapy was not available.

Conclusions

In a real-world trial with broad inclusion criteria enrolling patients with stable coronary disease or acute coronary syndromes, biodegradable polymer and permanent polymer DES are associated with similar clinical outcomes out to 3 years. In addition, in patients treated with permanent polymer DES, both EES and SES are associated with comparable outcomes over the same time period.

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Key Words: biodegradable ■ drug-eluting stent ■ everolimus ■ polymer ■ randomized trial ■ restenosis ■ sirolimus.

APPENDIX

For supplementary text, figures, and tables, please see the online version of this article.