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Long-term outcomes of biodegradable polymer versus durable polymer drug-eluting stents in patients with diabetes a pooled analysis of individual patient data from 3 randomized trials

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ABSTRACT

Background: There is ongoing debate on the optimal drug-eluting stent (DES) in diabetic patients with coronary artery disease. Biodegradable polymer drug-eluting stents (BP-DES) may potentially improve clinical outcomes in these high-risk patients. We sought to compare long-term outcomes in patients with diabetes treated with biodegradable polymer DES vs. durable polymer sirolimus-eluting stents (SES).

Methods: We pooled individual patient-level data from 3 randomized clinical trials (ISAR-TEST 3, ISAR-TEST 4 and LEADERS) comparing biodegradable polymer DES with durable polymer SES. Clinical outcomes out to 4 years were assessed. The primary end point was the composite of cardiac death, myocardial infarction and target-lesion revascularization. Secondary end points were target lesion revascularization and definite or probable stent thrombosis.

Results: Of 1094 patients with diabetes included in the present analysis, 657 received biodegradable polymer DES and 437 durable polymer SES. At 4 years, the incidence of the primary end point was similar with BP-DES versus SES (hazard ratio = 0.95, 95% CI = 0.74–1.21, $P = 0.67$). Target lesion revascularization was also comparable between the groups (hazard ratio = 0.89, 95% CI = 0.65–1.22, $P = 0.47$). Definite or probable stent thrombosis was significantly reduced among patients treated with BP-DES (hazard ratio = 0.52, 95% CI = 0.28–0.96, $P = 0.04$), a difference driven by significantly lower stent thrombosis rates with BP-DES between 1 and 4 years (hazard ratio = 0.15, 95% CI = 0.03–0.70, $P = 0.02$).

Conclusions: In patients with diabetes, biodegradable polymer DES, compared to durable polymer SES, were associated with comparable overall clinical outcomes during follow-up to 4 years. Rates of stent thrombosis were significantly lower with BP-DES.

1. Introduction

Biodegradable polymer-based DES, with controlled drug release followed by subsequent degradation of the polymer coating, has been developed with the aim to improve long-term clinical outcome after coronary stenting by rendering the stent surface similar to that of a bare metal stent. This design concept is hypothesized to reduce the incidence of late adverse events which have been linked to durable polymer coatings [1,2]. We previously showed superior efficacy of BP-DES versus durable polymer SES in a broadly inclusive patient population [3]. The pooled analysis showed a significant reduction of clinically indicated target lesion revascularization as well as definite stent thrombosis at 4 years, the latter was primarily driven by a significant reduction of very late definite stent thrombosis with biodegradable polymer DES compared to durable polymer SES.

Percutaneous coronary revascularization (PCI) in patients with a diagnosis of diabetes mellitus and coronary artery disease is associated with poorer outcomes in comparison with non-diabetic patients, both in terms of higher rates of stent thrombosis and increased need for repeat revascularization [4,5]. Although PCI with implantation of newer generation DES is overall markedly superior to first generation drug eluting stents, several randomized clinical trials and pooled

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analyses showed that these advantages are largely attenuated in diabetic patients [5–7].

Therefore, the definition of the optimal DES device in the high-risk subgroup of diabetics still remains an unsolved issue [6]. The present pooled analysis provides the possibility to evaluate whether the improved efficacy and safety offered by biodegradable polymer DES in comparison to durable polymer DES in all-comers can be extended to the high-risk subset of patients with diabetes.

2. Methods

2.1. Patient population

We performed a patient-level pooled analysis of the three largest multicenter, randomized clinical trials comparing biodegradable polymer DES with durable polymer SES for coronary revascularization: the ISAR-TEST 3 trial (ClinicalTrials.gov identifier: NCT00350454) [8], the ISAR-TEST 4 trial (ClinicalTrials.gov identifier: NCT00598676) [9] and the LEADERS trial (ClinicalTrials.gov identifier: NCT00389220) [10] and analyzed outcomes in the subset of patients with diabetes mellitus. The definition of diabetes mellitus was based on reported clinical history and/or active treatment with insulin or an oral hypoglycemic agent at admission, or abnormal fasting blood glucose or glucose tolerance test based on the World Health Organization criteria. From an overall population of 4062 patients in the included trials, a total of 1094 patients with diabetes were included in the present analysis; 657 of these were randomly allocated to treatment with biodegradable polymer DES (either Yukon PC Choice, Translumina, Hechingen, Germany or BioMatrix Flex, Biosensors Inc, Newport Beach, CA, USA), and 437 were allocated to treatment with durable polymer SES (Cypher Select, Cordis, Miami Lakes, FL, USA). Detailed descriptions of the design of the three trials are reported in the primary publications [8–10]. A summary of the principal trial characteristics was reported previously [3]. The definition of diabetes was consistent across all three clinical trials. Patients were followed up clinically out to 4 years after enrolment by the investigating sites.

2.2. Procedural and discharge medication

In all three trials, an oral loading dose of 300–600 mg clopidogrel was administered before or at the time of the PCI procedure. During the procedure, all patients received unfractionated heparin or bivalirudin, whereas the use of glycoprotein IIb/IIIa antagonists was left at the discretion of the operators. All patients were discharged on acetylsalicylic acid of at least 75 mg daily indefinitely and clopidogrel 75 mg daily for at least 6 months in the ISAR-TEST 3 and ISAR-TEST 4 trials, and at least 12 months in the LEADERS trial. Clinical follow-up was performed out to 4 years after enrolment.

2.3. End points and definitions

The pre-specified primary end point was the occurrence of major cardiac events (MACE), defined as the composite of cardiac death, myocardial infarction (MI) and target-lesion revascularization (TLR). Secondary end points were TLR (efficacy end point) and definite or probable stent thrombosis (safety end point). Cardiac death was defined as death due to immediate cardiac causes or complications related to the procedure, as well as any death in which a cardiac cause could not be excluded. Definitions of MI were consistent across the pooled trials; however, in the ISAR-TEST 4 trial target-vessel MI was adjudicated, whereas in the ISAR-TEST 3 and LEADERS trials any MI was included. TLR was defined as any clinically indicated repeat revascularization (percutaneous or surgical) of the target lesion. The definition of clinically indicated revascularization was consistent across the included trials. Stent thrombosis was defined in all 3 studies according to the Academic Research Consortium [11].

2.4. Trial quality assessment

All trials were assessed for bias using components recommended by the Cochrane Collaboration [12], including sequence generation of the allocation; allocation concealment; blinding of participants, personnel and outcome assessors; selective outcome reporting; and other sources of bias. Trials with high or unclear risk for bias for any one of the first three components were considered as trials with high risk of bias. Otherwise, they were considered as trials with low risk of bias.

2.5. Statistical analysis

Categorical data are presented as counts and proportions (%). Continuous data are presented as mean (±SD) or median [25th–75th percentiles]. Individual patient data were pooled and analyzed according to intention to treat. Survival analysis was performed using the Mantel–Cox method stratified by the trial. Trials in which the event of interest was not observed in either treatment group were omitted from the analysis of that event. In the event that only one of the treatment groups from a trial had no event of interest, then the estimated treatment effect estimate and its standard error were calculated after adding 0.5 to each cell of the 2×2 table for that trial [13]. Cochrane tests were used to assess heterogeneity across trials. Consistency between trials was measured by calculating the I^2 statistic—with values of 25%, 50% and 75% indicating low, moderate and high inconsistency, respectively [14]. Results were considered statistically significant at two-sided $P < 0.05$. Statistical analysis was performed using the Stata software package, version 9.2 (Stata Corp, College Station, TX, USA). Survival curves are presented as simple, non-stratified Kaplan–Meier curves and were constructed with the use of S-Plus software version 4.5 (Insightful Corporation, Seattle, WA, USA).

3. Results

All three included trials were assessed as low risk for bias, and no heterogeneity across trials was observed during the analysis. From a total of 4062 trial patients, 1094 patients with diabetes were included in the present analysis, of which 657 received biodegradable polymer DES and 437 received durable polymer SES.

A summary of included trials is shown in Table 1. Baseline characteristics were similar in both treatment groups and are summarized in Table 2. Clinical outcomes up to 4 years as well as landmark analyses are summarized in Table 3. At 4 years, the incidence of the primary end point was similar with BP-DES versus SES (25.0% vs. 26.6%; hazard ratio = 0.95, 95% CI = 0.74–1.21, $P = 0.67$; Fig. 1). Target lesion revascularization was also comparable between the groups (15.5% vs. 17.4%; hazard ratio = 0.89, 95% CI = 0.65–1.22, $P = 0.47$; Fig. 2). There were no differences between treatment groups in any of the individual elements of the composite primary end point. Definite or probable stent thrombosis occurred less often in those treated with BP-DES versus durable polymer SES (2.8% vs. 6.1%; hazard ratio = 0.52, 95%

Table 1
Summary of Included Trials.

	ISAR-TEST 3	ISAR-TEST 4	LEADERS
Number of patients Stent type	605 BP SES DP SES PF SES	2603 BP SES DP SES DP EES	1707 BP BES DP SES
Number of diabetic patients included in this analysis	111	569	414
Primary end point	In-stent late lumen loss	Composite of death, target vessel MI or clinically driven TLR at 12 months	Composite of cardiac death, MI or clinically driven TVR at 9 months
Inclusion criteria	Symptoms or evidence of ischemia	Symptoms of evidence of ischemia	No restriction
Clinical exclusion criteria	Acute MI, cardiogenic shock	Cardiogenic shock	None
Lesion exclusion criteria	In-stent restenosis, left main stem lesions, bypass graft lesions	In-stent restenosis, left main stem lesions, bypass graft lesions	None
Other exclusion criteria	Life expectancy <12 months pregnancy, known allergy to study medications	Life expectancy <12 months pregnancy, known allergy to study medications	Planned surgery <6 months of index procedure, known allergy to study medications

BES, biolimus-eluting stent; BP, biodegradable polymer; DP, durable polymer; EES, everolimus-eluting stent; MI, myocardial infarction; PF, polymer-free; SES, sirolimus-eluting stent; TLR, target lesion revascularization; TVR, target vessel revascularization.

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Table 2
Baseline characteristics.

	Biodegradable Polymer stent ($N = 657$)	Durable Polymer SES ($N = 437$)	*P* value
Age (years)	66.7 ± 10.2	67.3 ± 9.9	0.40
Male	481 (73.2%)	322(73.7%)	0.86
Insulin requiring	209 (31.8%)	157 (35.9%)	0.16
Hypertension	530 (80.7%)	344 (78.7%)	0.43
Hypercholesterolemia	460 (70.0%)	303 (69.3%)	0.81
Current smoker	97 (14.8%)	66 (15.1%)	0.88
Family history of coronary artery disease	240 (36.6%)	162 (44.0%)	0.86
History of MI	223 (33.9%)	138 (37.1%)	0.42
History of PCI	347 (52.8%)	219 (50.1%)	0.38
Previous CABG	88 (13.4%)	66 (15.1%)	0.42
Left ventricular ejection fraction (%)	51.8 ± 12.7	53 · 4 ± 13.0	0.05
Clinical presentation			0.92
ST-elevation MI	56 (8.5%)	34 (7.8%)	
Non ST-elevation MI	48 (7.3%)	33 (7.6%)	
Unstable angina	190 (28.9%)	121 (27.7%)	
Stable angina	363 (55.3%)	249 (57.0%)	
Lesion length (mm)	14.3 ± 8.3	14.1 ± 8.0	0.50
Reference vessel diameter (mm)	2.7 ± 0.6	2 · 7 ± 0.5	0.48
Diameter stenosis pre-intervention (%)	64.4 ± 15.5	63.3 ± 16.5	0.17
Diameter stenosis pre-intervention (%)	6.8 ± 9.9	8.1 ± 9.2	<0.01
Balloon diameter (mm)	3.0 ± 0.5	3.0 ± 0.5	0.62
Stented length (mm)	25.0 ± 14.6	24.9 ± 12.5	0.37

Data are mean ± SD or number (%). CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

CI = 0.28–0.96, $P = 0.04$), a difference driven by significantly lower stent thrombosis rates with BP-DES between 1 and 4 years (0.4% vs. 2.8%; hazard ratio = 0.15, 95% CI = 0.03–0.70, $P = 0.02$; see Fig. 3).

Table 3
Clinical outcomes through 4 years, overall and according to a landmark analysis at 1 year.

	Biodegradable polymer stent (%)	Durable polymer SES (%)	Hazard ratio (95% CI)	*P* value
Cardiac death, MI or TLR*	154/657 (25.0)	107/437 (26.6)	0.95 (0.74–1.21)	0.67
0 to 1 year	99/657 (15.3)	66/437 (15.6)	0.99 (0.72–1.35)	0.94
1 to 4 years	55/531 (11.4)	41/348 (13.1)	0.89 (0.59–1.33)	0.56
TLR	93/657 (15.5)	68/437 (17.4)	0.89 (0.65–1.22)	0.47
0 to 1 year	59/657 (9.4)	44/437 (10.6)	0.87 (0.59–1.29)	0.49
1 to 4 years	34/547 (6.8)	24/356 (7.6)	0.93 (0.55–1.56)	0.77
Definite or probable stent thrombosis	18/657 (2.8)	23/437 (6.1)	0.52(0.28–0.96)	0.04
0 to 1 year	16/657 (2.5)	14/437 (3.3)	0.75 (0.37–1.55)	0.44
1 to 4 years	2/590 (0.4)	9/386 (2.8)	0.15 (0.03–0.70)	0.02
Definite stent thrombosis	13/657 (2.0)	19/437 (5.0)	0.45 (0.22–0.92)	0.02
0 to 1 year	13/657 (2.0)	12/437 (2.8)	0.71 (0.33–1.57)	0.40
1 to 4 years	0/590 (0.0)	7/386 (2.2)	N/A	<0.001
Cardiac death or MI	88/657 (14.4)	62/437 (15.7)	0.95 (0.69–1.32)	0.76
0 to 1 year	53/657 (8.2)	32/437 (7.5)	1.11 (0.77–1.72)	0.65
1 to 4 years	35/574 (6.8)	30/381 (8.9)	0.79 (0.48–1.28)	0.33
Death	89/657 (14.7)	70/437 (17.4)	0.84 (0.62–1.15)	0.28
0 to 1 year	38/657 (5.9)	24/437 (5.7)	1.04 (0.62–1.73)	0.89
1 to 4 years	51/601 (9.4)	46/393 (12.4)	0.74 (0.50–1.10)	0.14
Cardiac death	50/657 (8.6)	36/437 (9.2)	0.92 (0.60–1.41)	0.71
0 to 1 year	21/657 (3.3)	18/437 (4.2)	0.77 (0.41–1.44)	0.41
1 to 4 years	29/601 (5.5)	18/393 (5.1)	1.08 (0.60–1.94)	0.80
MI	48/657 (7.7)	36/437 (9.3)	0.90 (0.58–1.38)	0.62
0 to 1 year	36/657 (5.6)	21/437 (4.9)	1.15 (0.67–1.97)	0.61
1 to 4 years	12/574 (2.2)	15/381 (4.6)	0.54 (0.25–1.15)	0.11

Percentages are Kaplan–Meier estimates. CI, confidence interval; MI, myocardial infarction; TLR, target-lesion revascularization; N/A, not applicable.
* Primary end point.

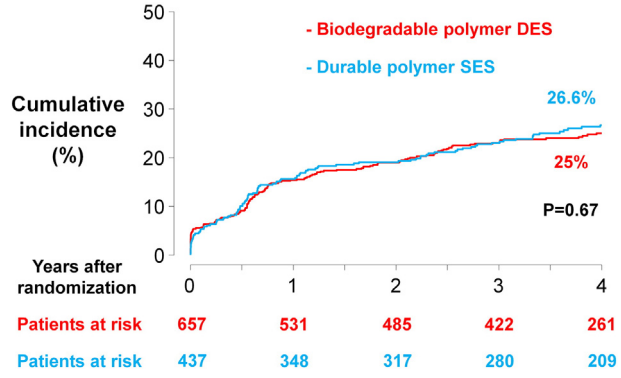

Fig. 1. Primary end point: cardiac death, myocardial infarction or TLR.

4. Discussion

In the present study, we analyzed individual patient data from 3 randomized trials comparing biodegradable polymer DES to durable polymer SES in 1094 patients with diabetes mellitus and followed these patients out to 4 years. The main finding was that while overall the risk of MACE and of TLR was equivalent in both groups, treatment with biodegradable polymer DES was associated with a significant reduction in definite or probable stent thrombosis, driven primarily by a statistically significant reduction in stent thrombosis occurring after one year.

DES achieve greater antirestenotic efficacy in comparison with bare metal stents at the cost of a delay in healing of the treated arterial segment [15–17]. Pathological studies of stent thrombosis cases have shown evidence of a persistent inflammatory response in the arterial wall and although direct evidence is somewhat surprisingly scant, durable polymer coatings have been heavily implicated in the etiology of this response [16,17]. Delayed arterial healing is a pathophysiological process characterized by persistent fibrin deposition, inflammatory cell infiltration (occasionally giant cell formation and eosinophilic infiltration due to hypersensitivity), delayed endothelial re-growth and ongoing platelet activation [15–17]. Moreover, clinical intravascular imaging studies have also shown evidence of incomplete stent apposition after DES implantation—a finding which appears to confer a higher risk of subsequent stent thrombosis [18,19].

Patients with diabetes are in pressing need of the most effective coronary stent. In particular numerous reports have highlighted diabetes mellitus as a risk factor for stent thrombosis [20–22]. This is due to a combination of factors ranging from adverse lesion morphology, higher levels of systemic inflammation and increased platelet reactivity and a higher prevalence of low response to thienopyridines [23,24]. Moreover, patients with diabetes seem to be at particular risk if dual

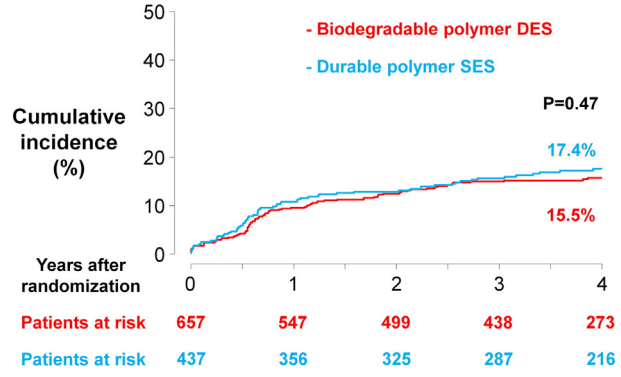

Fig. 2. Secondary efficacy end point: target lesion revascularization.

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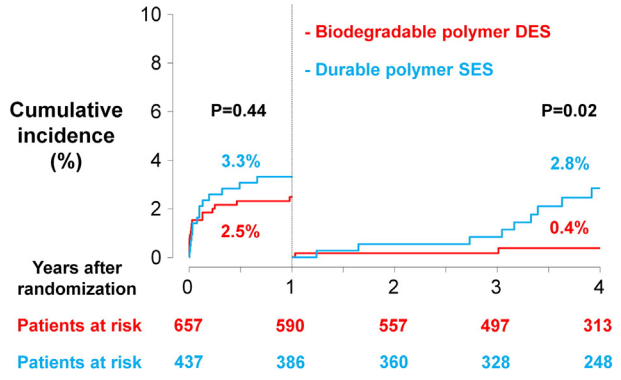

Fig. 3. Secondary safety end point: definite or probable stent thrombosis.

antiplatelet therapy is discontinued earlier than 6 months post intervention [4].

Against this background, biodegradable polymer DES represents an intuitively attractive approach for patients with diabetes [1]. Complete polymer biodegradation after drug elution means that the long-term vessel wall footprint is expected to resemble that of a bare metal stent. This is hypothesized to confer a lower risk of late stent thrombosis, an effect potentially magnified in patients with diabetes. Indeed a number of intravascular imaging studies show encouraging data regarding vessel healing after biodegradable polymer DES implantation in man [25,26].

Our study represents the first analysis of long-term outcomes in patients with diabetes treated with biodegradable polymer DES. First of all, our data confirmed higher rates of adverse events in diabetic patients in comparison to pooled 4-year data for the entire cohort from the trials, reflecting the increased risk following PCI in patients with diabetes. Indeed diabetic patients treated with SES had late ST rates above 0.8% per year. Second, we observed a statistically significant and likely also clinically relevant 48% reduction in definite or probable stent thrombosis with biodegradable versus durable polymer DES. Indeed, this reduction in stent thrombosis is significant not just in relative but also in absolute terms (3.3% reduction over 4 years). In addition, this reduction in stent thrombosis did not occur at the expense of reduced antirestenotic efficacy (TLR rates were comparable in both groups 15.5% versus 17.4%, respectively). In combination, these findings support the use of biodegradable polymer in patients with diabetes, suggesting a more marked reduction in stent thrombosis as compared with the reduction seen in the overall patient cohort [3]. For the first time, a new generation DES was able to transfer the beneficial effects shown in the overall population to the subgroup of diabetic patients.

4.1. Study limitations

The present study has several limitations. First, this was not a randomized clinical trial but a pooled analysis of a subgroup of individual patient data from three randomized clinical trials, neither of which performed stratified randomization according to the presence of diabetes. As a post hoc analysis, the results should be considered hypothesis generating. Second, whilst the present study comprises a large-scale comparison of biodegradable polymer vs. durable polymer DES in patients with diabetes mellitus, the sample size remains inadequate to exclude small differences in outcome between the 2 treatment groups. Third, although inclusion criteria were broad across, all 3 included trials there remained slight differences in the characteristics of patients enrolled in the individual trials. Fourth, only sirolimus-eluting durable polymer DES was included in the present comparison. Consequently, the results cannot be extended to other available durable polymer DES. Fifth, two different biodegradable polymer stents were included in the analysis, and although the coatings of both stents are similar, differences in polymer degradation and drug efficacy and release kinetics between the two stents may be expected. Finally, patients with acute coronary syndrome were treated with clopidogrel as newer ADP-receptor antagonists were largely unavailable at the time of enrollment.

5. Conclusion

The current pooled analysis of patients with diagnosed diabetes mellitus undergoing PCI with biodegradable polymer DES versus durable polymer SES demonstrates overall comparable clinical efficacy between the 2 stents. However, patients treated with biodegradable polymer DES were significantly less likely to suffer stent thrombosis at 4 years, a risk reduction driven primarily by a significant reduction in stent thrombosis late (>1 year) after device implantation.

These data support the preferential use of biodegradable polymer DES in patients with diabetes mellitus. The findings should be confirmed in a dedicated randomized controlled trial.

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Conflict of interest

B.M. has received educational and research support to the institution from Abbott, Cordis, Boston Scientific, and Medtronic; A.K. holds a patent related to the stent coating used on the biodegradable polymer DES studied in the ISAR-TEST 3 and ISAR-TEST 4 trials, A.K. reports having received lecture fees from Abbott, Biotronik, Cordis and Medtronic; S.W. has received research contracts to the institution from Abbott, Biosensors, Biotronik, Boston Scientific, Cordis, Medtronic, and St Jude. The other authors report no conflicts.

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