Original Contribution

Ten-Year Clinical Outcomes in Patients With Acute Coronary Syndrome Treated With Biodegradable, Permanent-Polymer or Polymer-Free Drug-Eluting Stents

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Abstract

Objectives. This study aimed to compare 10-year clinical outcomes in patients with acute coronary syndrome (ACS) treated with new-generation biodegradable-polymer (BP-DES), polymer-free (PF-DES), and permanent-polymer drug-eluting stents (PP-DES). **Methods.** We analyzed 10-year clinical outcomes for 2042 patients with ACS enrolled in the ISAR-TEST 4 and ISAR-TEST 5 randomized controlled trials. Patients were divided into 3 groups: new-generation PP-DES, BP-DES, and PF-DES. Endpoints of interest included a device-oriented composite endpoint (DOCE) and a patient-oriented composite endpoint (POCE) at 10 years. **Results.** BP-DES as compared with PP-DES demonstrated a lower DOCE frequency, but this did not meet statistical significance (BP-DES vs PP-DES, 35.4% vs 41.5%, respectively; adjusted hazard ratio (HR), 0.83; 95% confidence interval [CI], 0.68-1.00; *P*=.05). There was a significantly lower POCE frequency in patients treated with BP-DES compared with PP-DES (65.3% vs 69.0%, respectively; HR, 0.86; 95% CI, 0.75-0.99; *P*=.04). The relative frequency of the DOCE (41.4% vs 41.5%; HR, 0.97; 95% CI, 0.83-1.15; *P*=.76) and the POCE (66.8% vs 69.0%; HR, 0.99; 0.87-1.12; *P*=.82) were comparable in patients treated with PF-DES and PP-DES. **Conclusion.** In patients with ACS, BP-DES were associated with a lower relative frequency of a POCE compared with new-generation PP-DES at 10 years. The relative frequencies of both device- and patient-related outcomes were comparable in patients treated with PF-DES and PP-DES at 10 years.

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Key words: acute coronary syndrome, biodegradable polymer, long-term follow-up, percutaneous coronary intervention, permanent polymer, polymer-free

Drug-eluting stent (DES) implantation is the preferred treatment modality for the majority of patients with acute coronary syndrome (ACS).[1,2] While permanent-polymer DESs (PP-DESs) have been shown to be superior to bare-metal stents (BMSs) in patients with ACS,[3,4] concern has been raised that the presence of a permanent polymer may contribute to delayed healing and chronic inflammation in the vessel wall.[5-8] Furthermore, PP-DESs are associated with higher rates of neo-atherosclerosis in comparison with BMSs.[9] Both of these pathophysiologies may be associated with the occurrence of late adverse events after percutaneous coronary intervention (PCI).

This led to the development of biodegradable-polymer DES (BP-DES) and polymer-free DES (PF-DES) platforms. While it has been hypothesized that these newer stent technologies would lead to improved outcomes compared with PP-DES, the evidence in this regard has been mixed. Patients with ACS have been shown to demonstrate increased levels of inflammation post PCI as compared with patients with stable coronary artery disease

(CAD).[10,11] Therefore, it is logical to consider that BP-DES and PF-DES devices may confer a clinical advantage compared with PP-DES in this specific patient group.

It has been suggested that the benefit of enhanced polymer strategies may emerge with longer-term follow-up. Traditionally, stent trials have focused on shorter-term outcomes. However, in recent years, increasing consideration has been given to long-term outcomes post PCI.[12,13] This represents an important shift in focus to the safety and efficacy of these devices over the lifespan of the patient. A comprehensive analysis of 10-year outcomes in all 3 newer-generation DES polymer types (PP, BP, and PF) in patients with ACS has not been performed. As such, the long-term relative efficacy of these stent platforms in patients with ACS remains uncertain.

Against this background, the objective of this analysis was to assess 10-year clinical outcomes in patients with ACS treated with new-generation PP-, BP-, and PF-DES platforms.

Methods

Study population. Patient-level data from 2 randomized, controlled trials (ISAR-TEST 4 and ISAR-TEST 5) were pooled. The full designs of these 2 trials (study populations, methods, endpoints) have been previously reported.[14,15] In brief, ISAR-TEST 4 compared 3 limus-eluting stents with different polymer strategies in 2603 patients. The 3 treatment arms were: (1) new-generation BP-based sirolimus-eluting stent (BP-SES) (n = 1299); (2) new-generation PP-based everolimus-eluting stent (PP-EES) (n = 652); and (3) early-generation PP-SES (n = 652). The ISAR-TEST 5 trial enrolled 3002 patients and compared outcomes between new-generation polymer-free sirolimus and probucol-eluting stent (PF-SES; n = 2002), and new-generation PP zotarolimus-eluting stent (PP-ZES) (n = 1000). We included patients from ISAR-TEST 4 and ISAR-TEST 5 who presented with ACS (defined as either ST–segment-elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction [NSTEMI], or unstable angina [UA]) in this analysis. We excluded patients in the early-generation PP-SES group from ISAR-TEST 4. Therefore, the 3 groups in this analysis were: (1) new-generation PP-EES and PP-ZES (the PP-DES group); (2) BP-based SES devices (the BP-DES group); and (3) polymer-free sirolimus and probucol-eluting stents (the PF-DES group). ACS patients in this study were further subclassified as either acute myocardial infarction (STEMI/NSTEMI) or UA. Patients for both trials were enrolled at 2 centers in Munich, Germany. Both trials were prospectively designed with similar methods and endpoint definitions. Statistical programming algorithms and databases were also similar and allowed pooling of data sets. This study conforms to the Declaration of Helsinki and the study protocol was approved by the ethics committee of the 2 participating centers in Munich, Germany (Deutsches Herzzentrum München and 1. Medizinische Klinik, Klinikum rechts der ISAR). Ten-year clinical results of both trials have been reported previously.[12,13]

Enrollment criteria. Enrollment criteria for both studies were similar and have been previously reported.[14,15] Patients older than 18 years with ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of ≥50% *de novo* stenosis located in the native coronary vessels were considered eligible. Patients with a target lesion in the left main stem or in cardiogenic shock were considered ineligible for both studies.

Endpoints and definitions. Endpoints of interest for this analysis included a device-oriented composite endpoint (DOCE) consisting of cardiac death, target-vessel myocardial infarction (TV-MI), or target-lesion revascularization (TLR) and a patient-oriented composite endpoint (POCE), consisting of all-cause death, any MI, or any revascularization. Additional endpoints included the individual components of the composite endpoints and definite or probable stent thrombosis. In-depth descriptions of the study endpoint definitions have been published previously.[14,15]

Statistical analysis. Continuous data are presented as means ± standard deviations or medians and interquartile ranges. Categorical data are presented as counts and proportions (%). Data distribution was tested for normality by using the Kolmogorov-Smirnov test for goodness of fit. Differences between groups were checked for significance using an analysis of variance test (ANOVA) for continuous data. Depending on the data distribution, chi-squared test or Fisher's exact test were used to check for differences between categorical variables. Survival was analyzed with the Kaplan-Meier method. Hazard ratios (HRs) were calculated using a Cox proportional hazards model after checking for fulfillment of the proportional hazards assumption as per the method of Grambsch and Therneau.[16] The analysis of endpoints other than all-cause mortality also accounted for the competing risk of death. The analysis of the outcomes of interest was performed on an intention-to-treat basis with adjustment for the following variables: multivessel disease, number of lesions, clinical presentation (acute MI), vessel stented, lesion length, preprocedure percentage stenosis, and total stented length. Statistical analysis was performed using the R 3.6.0 Statistical Package (R Foundation for Statistical Computing). A 2-tailed *P*-value of <.05 was taken to confer statistical significance.

Results

We included 2042 patients with ACS in the current analysis. This represents 36.4% of the total cohort of patients enrolled in the ISAR-TEST 4 and ISAR-TEST 5 trials. Of these 2042 patients, 690 (33.8%) were treated with PP-DES, 541 (26.5%) with BP-DES, and 811 (39.7%) with PF-DES. This information is summarized in the patient flow diagram (**Supplemental Figure S1**).

TABLE 1. Baseline characteristics stratified by stent type.

Characteristics	Biodegradable-Polymer Stent (n = 541 Patients)	Polymer-Free Stent (n = 811 Patients)	Permanent-Polymer Stent (n = 690 Patients)	*P*-Value
Age (years)	66.7 ± 11.9	67.5 ± 12.1	67.1 ± 11.1	.48
Female	161 (29.8%)	217 (26.8%)	171 (24.8%)	.15
Diabetes mellitus	164 (30.3%)	215 (26.5%)	200 (29.0%)	.28
Insulin dependent	53 (9.8%)	87 (10.7%)	73 (10.6%)	.85
Hypertension	330 (61.0%)	512 (63.1%)	418 (60.6%)	.55
Current smoker	117 (21.6%)	192 (23.7%)	152 (22.0%)	.62
Hypercholesterolemia	327 (60.4%)	455 (56.1%)	420 (60.9%)	.12
Body mass index (kg/m^2)[a]	27.1 ± 4.4	27.6 ± 4.7	27.4 ± 4.4	.13
Prior myocardial infarction	137 (25.3%)	200 (24.7%)	174 (25.2%)	.95
Prior aortocoronary bypass surgery	51 (9.4%)	57 (7.0%)	63 (9.1%)	.20
Number of diseased coronary vessels				.02
1 vessel	79 (14.6%)	176 (21.7%)	117 (17.0%)	
2 vessels	153 (28.3%)	205 (25.3%)	192 (27.8%)	
3 vessels	309 (57.1%)	430 (53.0%)	381 (55.2%)	
Number of lesions	1.3 ± 0.6	1.5 ± 0.7	1.4 ± 0.6	<.001
Clinical presentation				<.001
Acute myocardial infarction	167 (30.9%)	446 (55.0%)	291 (42.2%)	
Unstable angina	374 (69.1%)	365 (45.0%)	399 (57.8%)	
Ejection fraction (%)[a]	50.7 ± 11.7	51.3 ± 11.7	50.6 ± 12.1	.50
Relook angiogram	398 (73.6%)	607 (74.8%)	509 (73.8%)	.84

Data presented as mean ± standard deviation or count (%).
[a]Missing continuous data: body mass index was not available in 5 patients (1 in the permanent-polymer group, 3 in the biodegradable-polymer group, and 1 in the polymer-free group); ejection fraction was not available in 269 patients (85 in the permanent-polymer group, 72 in the biodegradable-polymer group and 112 in the polymer-free group). The remaining continuous data were complete.

Baseline and procedural characteristics. Baseline characteristics for the 3 groups are shown in **Table 1** and procedural characteristics for the 3 groups are shown in **Table 2**. The 3 groups were well matched with respect to their comorbidities and past medical histories. There was a statistically significant difference between the 3 groups with regard to the frequency of acute MI as the mode of clinical presentation (BP-DES vs PF-DES vs PP-DES, 30.9% vs 55.0% vs 42.2%, respectively; *P*<.001).

Clinical outcomes at 10 years. Clinical outcomes at 10 years in the PP-DES, BP-DES, and PF-DES groups are summarized in **Table 3**.

Device-oriented composite endpoint at 10 years. The DOCE was composed of cardiac death, TV-MI, or TLR at 10 years. The DOCE occurred in 268 of 690 patients treated with PP-DES, 178 of 541 patients treated with BP-DES, and 313 of 811 patients treated with PF-DES at 10 years. There was a signal toward a lower frequency of DOCE in patients treated with BP-DES compared with those treated with PP-DES, but this did not meet statistical significance (BP-DES vs PP-DES, 35.4% vs 41.5%, respectively; adjusted HR, 0.83; 95% confidence interval [CI], 0.68-1.00; *P*=.05). There was no difference between the PF-DES group and PP-DES group with regard to the relative frequency of the DOCE at 10 years (PF-DES vs PP-DES, 41.4% vs 41.5%, respectively; HR, 0.97; 95% CI, 0.83-1.15; *P*=.76). This is shown in **Figure 1**.

Individual components of the device-oriented composite endpoint at 10 years. The relative frequency of cardiac mortality was comparable for both the BP-DES vs PP-DES (21.0% vs 23.7%, respectively; HR, 0.89; 95% CI, 0.69-1.15; *P*=.38) and PF-DES vs PP-DES (24.8% vs 23.7%, respectively; HR, 1.00; 95% CI, 0.80-1.24; *P*=.98) comparisons. TV-MI was also comparable for BP-DES vs PP-DES (5.4% vs 4.8%, respectively; HR, 1.17; 95% CI, 0.69-1.96;

TABLE 2. Angiographic and procedural characteristics stratified by stent type.

	Biodegradable-Polymer Stent (n = 685 Lesions)	Polymer-Free Stent (n = 1214 Lesions)	Permanent-Polymer Stent (n = 969 Lesions)	*P*-Value
Target vessel				.02
Left anterior descending coronary artery	319 (46.6%)	585 (48.2%)	438 (45.2%)	
Left circumflex coronary artery	181 (26.4%)	248 (20.4%)	235 (24.3%)	
Right coronary artery	185 (27.0%)	381 (31.4%)	296 (30.5%)	
Chronic total occlusion	35 (5.1%)	66 (5.4%)	45 (4.6%)	.70
Complex morphology (B2/C)	547 (79.9%)	996 (82.0%)	770 (79.5%)	.26
Lesion length (mm)	15.2 ± 8.5	16.7 ± 9.5	17.3 ± 9.7	<.001
Vessel size (mm)	2.8 ± 0.5	2.8 ± 0.5	2.8 ± 0.5	.63
Total stented length (mm)	23.8 ± 10.6	26.2 ± 12.1	27.2 ± 12.1	<.001
Percent stenosis, pre procedure (%)	69.2 ± 17.0	71.3 ± 17.3	70.9 ± 16.9	.03
Percent stenosis, post procedure (%)	11.8 ± 8.8	12.3 ± 8.0	11.3 ± 7.8	.02
Balloon diameter (mm)	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	.86

Data presented as mean ± standard deviation or count (%).

TABLE 3. Clinical outcomes at 10 years stratified by stent type.

	BP-DES (n = 541)	PF-DES (n = 811)	PP-DES (n = 690)	BP-DES vs PP-DES		PF-DES vs PP-DES	
				HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Device-oriented composite endpoint	178 (35.4%)	313 (41.4%)	268 (41.5%)	0.83 (0.68-1.00)	.05	0.97 (0.83-1.15)	.76
Cardiac mortality	101 (21.0%)	181 (24.8%)	148 (23.7%)	0.89 (0.69-1.15)	.38	1.00 (0.80-1.24)	.98
Target-vessel myocardial infarction	28 (5.4%)	32 (4.0%)	32 (4.8%)	1.17 (0.69-1.96)	.56	0.89 (0.54-1.47)	.66
Target-lesion revascularization	81 (15.7%)	154 (19.9%)	129 (19.5%)	0.81 (0.61-1.08)	.15	1.03 (0.81-1.31)	.80
Patient-oriented composite endpoint	337 (65.3%)	518 (66.8%)	457 (69.0%)	0.86 (0.75-.99)	.04	0.99 (0.87-1.12)	.82
All-cause mortality	182 (37.2%)	260 (34.8%)	229 (36.1%)	1.02 (0.84-1.25)	.83	0.95 (0.79-1.14)	.57
Any myocardial infarction	39 (7.6%)	49 (6.2%)	46 (7.0%)	1.11 (0.72-1.71)	.65	0.95 (0.63-1.43)	.79
Any revascularization	206 (39.3%)	352 (44.5%)	292 (43.5%)	0.84 (0.70-1.00)	.06	1.06 (0.91-1.25)	.45
Stent thrombosis							
Definite or probable	8 (1.5%)	16 (2.0%)	15 (2.3%)	0.77 (0.32-1.85)	.56	0.86 (0.42-1.77)	.69
Definite	3 (0.6%)	9 (1.2%)	4 (0.6%)	1.22 (0.27-5.58)	.80	1.94 (0.59-6.40)	.28

Data are shown as number of events with Kaplan-Meier estimates (%) for primary endpoint and death or cumulative incidence (%) after accounting for competing risk for the remaining endpoints.
CI = confidence interval; BP = biodegradable polymer; DES = drug-eluting stent; PF = polymer free; PP = permanent polymer.

P=.56) and for PF-DES vs PP-DES (4.0% vs 4.8%, respectively; HR, 0.89; 95% CI, 0.54-1.47; *P*=.66). There were no significant differences in the relative frequency of TLR for either the BP-DES vs PP-DES (15.7% vs 19.5%, respectively; HR, 0.81; 95% CI, 0.61-1.08; *P*=.15) or the PF-DES vs PP-DES (19.9% vs 19.5%, respectively; HR, 1.03; 95% CI, 0.81-1.31; *P*=.80) comparisons.

Patient-oriented composite endpoint at 10 years. The POCE was composed of all-cause death, any MI, or any revascularization at 10 years. The POCE occurred in 457 of 690 patients treated with PP-DES, 337 of 541 patients treated with BP-DES, and 518 of 811 patients treated with PF-DES at 10 years. There was a lower frequency of the POCE in patients treated with BP-DES compared with PP-DES (65.3% vs 69.0%, respectively; HR, 0.86; 95% CI, 0.75-0.99; *P*=.04). There were no statistically significant differences between the PF-DES and PP-DES groups with regard to the relative frequency of the POCE (66.8% vs 69.0%, respectively; HR, 0.99; 95% CI, 0.87-1.12; *P*=.82). This is shown in **Figure 2**.

Individual components of the patient-oriented composite endpoint at 10 years. All-cause mortality occurred in 229 of 690 patients treated with PP-DES, 182 of 541 patients treated with BP-DES, and 260 of 811 patients treated with PF-DES at 10 years (BP-DES vs PP-DES, 37.2% vs 36.1%, respectively; HR, 1.02; 95% CI, 0.84-1.25; *P*=.83; PF-DES vs PP-DES, 34.8% vs 36.1%, respectively; HR, 0.95; 95% CI, 0.79-1.14; *P*=.57). The occurrence of any MI was comparable for both the BP-DES vs PP-DES and PF-DES vs PP-DES comparisons (BP-DES vs PP-DES, 7.6% vs 7.0%, respectively; HR, 1.11; 95% CI, 0.72-1.71; *P*=.65; PF-DES vs PP-DES, 6.2% vs 7.0%, respectively; HR, 0.95; 95% CI, 0.63-1.43; *P*=.79). The incidence of any revascularization was numerically lower in the BP-DES group compared with the PP-DES group, but this did not meet statistical significance (39.3% vs 43.5%, respectively; HR, 0.84; 95% CI, 0.70-1.00; *P*=.06). There was no statistically significant difference in the relative frequencies of this endpoint between the PF-DES and PP-DES groups (44.5% vs 43.5%, respectively; HR, 1.06; 95% CI, 0.91-1.25; *P*=.45).

Stent thrombosis at 10 years. Definite or probable ST occurred in 39 of 2042 patients at 10 years. There was no statistically significant difference in the relative frequency of this endpoint for either the BP-DES vs PP-DES or the PF-DES vs PP-DES comparisons (BP-DES vs PP-DES, 1.5% vs 2.3%, respectively; HR, 0.77; 95% CI, 0.32-1.85; *P*=.56; PF-DES vs PP-DES, 2.0% vs 2.3%, respectively; HR, 0.86; 95% CI, 0.42-1.77; *P*=.69). Definite ST occurred in 16 of 2042 patients at 10 years. There was no statistically significant difference in the relative frequency of this endpoint for either the BP-DES vs PP-DES or the PF-DES vs PP-DES comparisons (BP-DES vs PP-DES, 0.6% vs 0.6%; HR, 1.22; 95% CI, 0.27-5.58; *P*=.80; PF-DES vs PP-DES, 1.2% vs 0.6%; HR, 1.94; 95% CI, 0.59-6.40; *P*=.28).

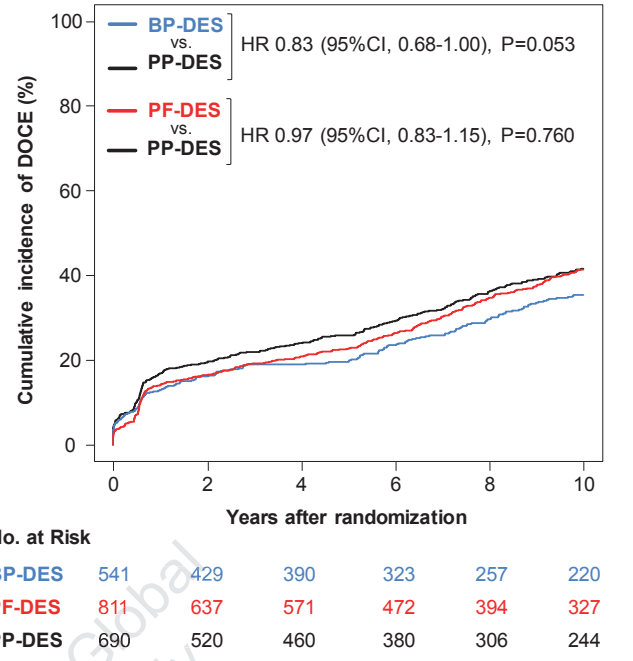

FIGURE 1. Ten-year cumulative incidence of the device-oriented composite endpoint as per stent type. BP = biodegradable polymer; CI = confidence interval; DES = drug-eluting stent; DOCE = device-oriented composite endpoint; HR = hazard ratio; PF = polymer free; PP = permanent polymer.

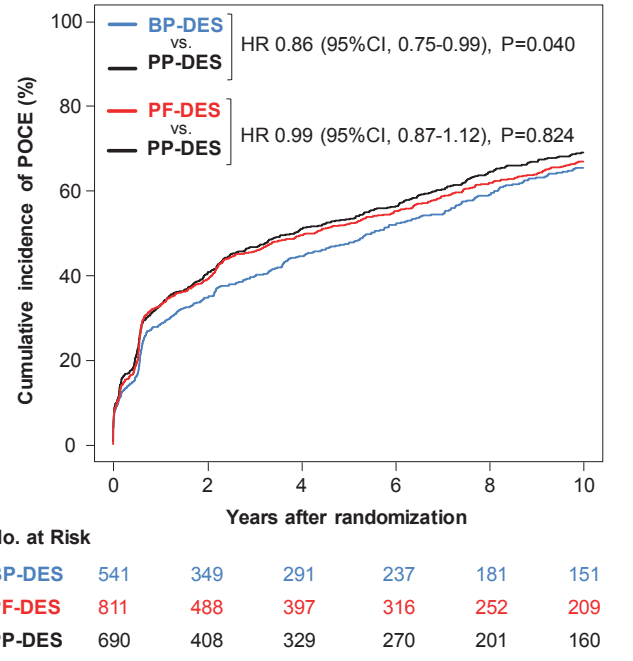

FIGURE 2. Ten-year cumulative incidence of the patient-oriented composite endpoint as per stent type. BP = biodegradable polymer; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; PF = polymer free; POCE = patient-oriented composite endpoint; PP = permanent polymer.

Analysis of outcomes as per clinical presentation. We also performed an unadjusted analysis to assess clinical outcomes in patients treated with PP-DES, BP-DES, and PF-DES as stratified by mode of clinical presentation (acute MI or UA).

BP-DES vs PP-DES. With regard to the DOCE, the HR for BP-DES vs PP-DES was similar for patients presenting with both acute MI (HR, 0.80; 95% CI, 0.58-1.10; *P*=.17) and UA (HR, 0.82; 95% CI, 0.65-1.05; *P*=.11). With regard to the POCE, there was a significant reduction in the frequency of this endpoint for patients with acute MI treated with BP-DES compared with PP-DES (HR, 0.78; 95% CI, 0.61-0.99; *P*<.05). In patients presenting with UA, outcomes were comparable between the BP-DES and PP-DES groups (HR, 0.93; 95% CI, 0.78-1.11; *P*=.41).

PF-DES vs PP-DES. The frequency of the DOCE was comparable in both the PF-DES and PP-DES groups for patients with acute MI (HR, 0.81; 95% CI, 0.64-1.03; *P*=.09) and UA (HR, 1.11; 95% CI, 0.89-1.38; *P*=.38). Outcomes with regard to the POCE were also comparable for both the PF-DES and PP-DES groups in patients with AMI and UA. These data are summarized in **Supplemental Table S1** and **Supplemental Table S2**.

Discussion

The main findings of this study can be summarized as follows. In patients treated with DES implantation for ACS, BP-DES resulted in a lower relative frequency of the POCE at 10 years, compared with PP-DES. There was also a signal toward a lower relative frequency of the DOCE in patients treated with BP-DES compared with PP-DES, although this did not reach statistical significance. PF-DES showed comparable clinical outcomes to PP-DES with regard to both the DOCE and the POCE at 10 years. The relative frequencies of definite or probable stent thrombosis did not differ for the BP-DES vs PP-DES or PF-DES vs PP-DES comparisons and were low overall, with a cumulative incidence of <2% at 10-year follow-up.

These data suggest that in patients with ACS treated with DES implantation, BP-DES is superior to PP-DES with regard to the frequency of a POCE (all-cause death, any MI, or any revascularization), with a signal toward a lower frequency of a DOCE (defined as cardiac death, TV-MI, or ischemia-driven TLR) at 10 years. This appears to be driven by a lower frequency of both target-lesion and any revascularization for patients treated with BP-DES compared with PP-DES in our analysis. It is recognized that delayed vessel healing and persistent vessel-wall inflammation may increase the risk of major adverse cardiac events in patients post PCI.[7] Optical coherence tomography analysis of patients post STEMI has demonstrated that patients treated with BP-DES demonstrate superior vessel-healing status compared with PP-DES at 1 year post PCI.[17] Given that patients with ACS demonstrate increased levels of inflammatory markers post PCI, it stands to reason that this patient cohort may derive particular benefit from treatment with BP-DES.

There are limited data on long-term outcomes with BP-DES in patients presenting with ACS. The BIOSTEMI trial reported that in patients with STEMI treated with primary PCI, BP-SES is superior to PP-EES with regard to target-lesion failure at 1 year.[18] This finding was primarily driven by reduced TLR in the BP-DES group. These data built on previous results reported in the BIO-SCIENCE study, where a prespecified stratified analysis reported that the BP-DES was associated with a significant benefit in the subgroup of patients with STEMI.[19] Pooled analysis of the ISAR-TEST 3, ISAR-TEST 4, and LEADERS trials reported that in patients with STEMI, BP-DES resulted in a significant reduction in major adverse cardiovascular events, primarily driven by a lower frequency of TLR. Our study is notable in that it offers the longest-term follow-up data for patients presenting with ACS who are treated with BP-DES.

Previous studies suggested that the use of BP-DES may result in incremental improvements in clinical outcomes in comparison with PP-DES. A pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials demonstrated that BP-DES reduced the risk of stent thrombosis and TLR at 4 years compared with PP-DES.[21] However, in this analysis, the PP-DES comparator was an early-generation durable-polymer SES. Our current analysis compares the BP-DES with new-generation PP-EES and PP-ZES and therefore may be more relevant to current clinical practice. In the BIOFLOW V trial, patients were randomized to a BP-SES or a PP-EES.[22] The trial showed non-inferiority of the BP-SES at 12-month follow-up. At 3 years, the BP-SES group demonstrated significantly lower rates of target-lesion failure, TV-MI, ischemia-driven TLR, and stent thrombosis.[23] However, the majority of patients in this study had either stable or unstable angina, with only ~12.1% of patients presenting with an elevation in cardiac enzymes at baseline. In addition, patients presenting with STEMI were excluded from this analysis. Conversely, the BIO-RESORT trial reported that at 3-year follow-up, everolimus and sirolimus-eluting BP-DESs showed comparable clinical outcomes to a zotarolimus-eluting PP-DES in an all-comers population, in which over two-thirds presented with ACS.[24,25]

When analyzing the mixed results of these studies, it is important to consider that there were important differences in the stent platforms investigated with regard to the antiproliferative agent eluted, strut thickness, and polymer composition. This leads to significant heterogeneity between the studies and as such, direct comparisons are difficult to make. However, taken as a whole, these data suggest that BP-DES may lead to improved outcomes compared with PP-DES, particularly when biodegradable polymer technology is combined with a thin-strut design.

It has previously been demonstrated that PF-DESs are superior to BMSs for patients with ACS undergoing PCI.[26] In this analysis, the PF-DES group demonstrated comparable outcomes to the PP-DES group with respect to both the DOCE and POCE at 10 years. This is consistent with a previous meta-analysis comparing the

2 stent platforms in patients with ACS.[27] In addition, it is notable that the frequency of definite stent thrombosis in the PF-DES group was double that in the PP-DES and BP-DES groups in this study. As such, our analysis does not support the hypothesis that treatment with PF-DES confers an advantage compared with PP-DES in regard to long-term outcomes for patients with ACS.

The overall frequency of stent thrombosis in this analysis deserves further discussion. The relative frequency of definite/probable stent thrombosis for the entire cohort at 10 years was <2% and comparable between the 3 groups. However, this analysis was not adequately powered to rule out meaningful differences between the groups with regard to this endpoint. Notably, there were no definite or probable stent thrombosis events in the BP-DES group from 2 to 10 years. Both PP-DES and BP-DES groups had a definite stent thrombosis frequency of <1% at 10-year follow-up, highlighting the reduction in the occurrence of this adverse clinical outcome with new-generation stent technology.

While the frequency of stent thrombosis in our analysis was impressively low, the same cannot be said for the relative frequency of DOCE and POCE at 10 years. The DOCE occurred in over 30% of patients and the POCE in over 60% of patients at 10 years, irrespective of the stent polymer type employed. This is a pertinent reminder that ACS patients treated with PCI represent a high-risk cohort and require aggressive secondary prevention measures in order to reduce the frequency of recurrent major adverse cardiovascular events. Achieving this goal will undoubtedly require novel pharmacotherapeutic strategies in addition to iterative improvements in stent technology.

Overall, this analysis provides novel long-term data on patients with ACS treated with the 3 commercially available stent polymer types. Our data show that in patients with ACS, treatment with BP-DES was superior to newer-generation PP-DES with regard to a lower relative frequency of POCE at 10 years. In addition, there was a signal toward a lower frequency of DOCE at 10 years for the BP-DES group. Dedicated randomized controlled trials with long-term follow-up may be useful to provide further evidence to support these findings.

Study limitations. The major limitation of this analysis is that it is not a randomized clinical trial, but a *posthoc* analysis of pooled data from 2 randomized controlled trials. In addition, multiple comparisons were performed in this analysis, potentially increasing the risk of type 1 error. As such, the results should be regarded as hypothesis generating and interpreted with caution. Given that the patient data from 2 trials were pooled in this analysis, we performed an adjusted analysis. However, we cannot rule out the possibility that important differences between the groups may remain despite adjustment for multiple variables. Patients with ACS constituted only 36.4% of the total cohort enrolled in the ISAR-TEST 4 and ISAR-TEST 5 trials; therefore, this analysis is relatively underpowered to assess for differences in individual endpoints. A final limitation of this analysis is the absence of data on rates of dual-antiplatelet therapy and cardiovascular secondary prevention measures up to 10 years.

Conclusion

In patients with ACS, the BP-DES group was associated with a lower relative frequency of patient-related clinical outcomes compared with new-generation PP-DES at 10 years. The relative frequency of both device- and patient-related outcomes was comparable in patients treated with PF-DES and PP-DES at 10 years.

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Supplemental Materials

SUPPLEMENTAL TABLE S1. Clinical outcomes at 10 years stratified by stent type in patients with acute myocardial infarction.

	Acute Myocardial Infarction (n = 904)			BP-DES vs PP-DES		PF-DES vs PP-DES	
	BP-DES (n = 167)	PF-DES (n = 446)	PP-DES (n = 291)	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Device-oriented composite endpoint	58 (37.4%)	156 (37.5%)	116 (42.6%)	0.80 (0.58-1.10)	.17	0.81 (0.64-1.03)	.09
Cardiac mortality	39 (25.6%)	101 (24.9%)	74 (27.4%)	0.87 (0.59-1.29)	.49	0.84 (0.62-1.13)	.25
Target-vessel myocardial infarction	5 (3.2%)	16 (3.7%)	14 (5.1%)	0.61 (0.22-1.70)	.35	0.72 (0.35-1.47)	.36
Target-lesion revascularization	21 (13.0%)	70 (16.4%)	50 (18.2%)	0.71 (0.43-1.18)	.18	0.87 (0.61-1.25)	.45
Patient-oriented composite endpoint	97 (60.7%)	276 (64.4%)	191 (68.7%)	0.78 (0.61-0.99)	.05	0.88 (0.73-1.06)	.19
All-cause mortality	57 (36.9%)	149 (36.0%)	106 (39.0%)	0.90 (0.65-1.24)	.50	0.87 (0.68-1.11)	.27
Any myocardial infarction	8 (5.2%)	25 (5.8%)	19 (6.8%)	0.71 (0.31-1.63)	.42	0.82 (0.45-1.50)	.52
Any revascularization	51 (30.9%)	184 (42.1%)	115 (40.9%)	0.72 (0.52-1.00)	.05	1.00 (0.80-1.27)	.97
Stent thrombosis							
Definite or probable	4 (2.4%)	10 (2.3%)	9 (3.3%)	0.78 (0.24-2.53)	.68	0.71 (0.29-1.74)	.45
Definite	2 (1.2%)	6 (1.4%)	1 (0.3%)	3.54 (0.32-39.04)	.30	3.82 (0.46-31.75)	.21

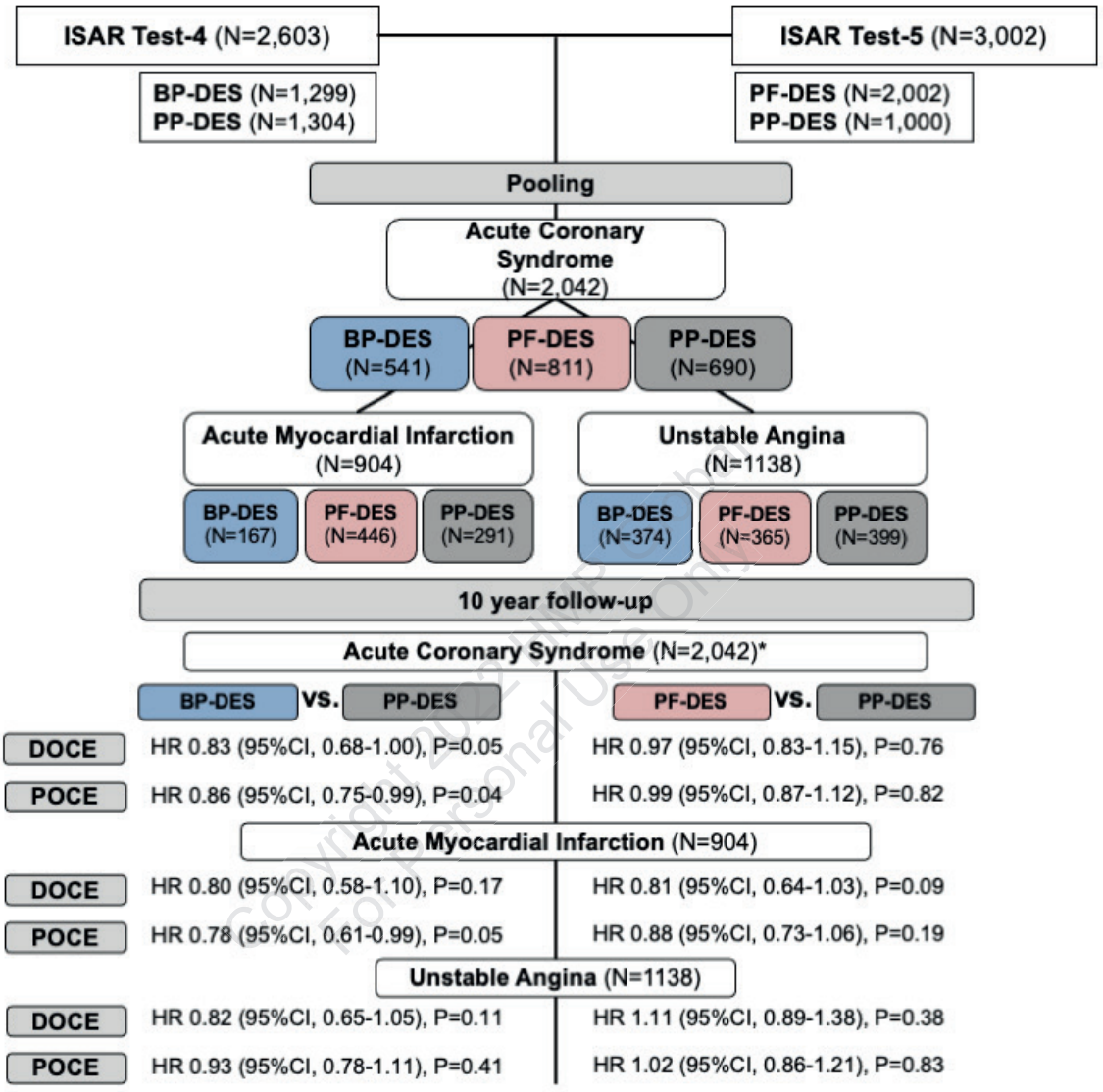
Data are shown as number of events with Kaplan-Meier estimates (%) for primary endpoint and death or cumulative incidence (%) after accounting for competing risk for the remaining endpoints.
CI = confidence interval; BP = biodegradable polymer; DES = drug-eluting stent; HR = hazard ratio; PF = polymer free; PP = permanent polymer.

SUPPLEMENTAL TABLE S2. Clinical outcomes at 10 years stratified by stent type in patients with unstable angina.

	Unstable Angina (n = 1138)			BP-DES vs PP-DES		PF-DES vs PP-DES	
	BP-DES (n = 374)	PF-DES (n = 365)	PP-DES (n = 399)	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Device-oriented composite endpoint	120 (34.5%)	157 (46.2%)	152 (40.6%)	0.82 (0.65-1.05)	.11	1.11 (0.89-1.38)	.38
Cardiac mortality	62 (19.0%)	80 (24.6%)	74 (21.0%)	0.95 (0.68-1.33)	.75	1.15 (0.84-1.58)	.38
Target vessel myocardial infarction	23 (6.4%)	16 (4.4%)	18 (4.6%)	1.38 (0.74-2.56)	.31	0.97 (0.50-1.91)	.93
Target lesion revascularization	60 (16.9%)	84 (24.2%)	79 (20.4%)	0.79 (0.56-1.10)	.16	1.14 (0.84-1.55)	.40
Patient-oriented composite endpoint	240 (67.4%)	242 (69.6%)	266 (69.0%)	0.93 (0.78-1.11)	.41	1.02 (0.86-1.21)	.83
All-cause mortality	125 (37.3%)	111 (33.4%)	123 (33.9%)	1.14 (0.88-1.46)	.32	0.97 (0.75-1.25)	.79
Any myocardial infarction	31 (8.7%)	24 (6.7%)	27 (7.1%)	1.25 (0.75-2.10)	.40	0.97 (0.56-1.69)	.93
Any revascularization	155 (43.0%)	168 (47.4%)	177 (45.3%)	0.90 (0.72-1.11)	.32	1.05 (0.85-1.29)	.66
Stent thrombosis							
Definite or probable	4 (1.1%)	6 (1.7%)	6 (1.5%)	0.72 (0.20-2.54)	.60	1.09 (0.35-3.37)	.89
Definite	1 (0.3%)	3 (0.9%)	3 (0.8%)	0.36 (0.04-3.46)	.38	1.09 (0.22-5.38)	.92

Data are shown as number of events with Kaplan-Meier estimates (%) for primary endpoint and death or cumulative incidence (%) after accounting for competing risk for the remaining endpoints.
CI = confidence interval; BP = biodegradable polymer; DES = drug-eluting stent; HR = hazard ratio; PF = polymer-free; PP = permanent polymer.

Supplemental Materials



SUPPLEMENTAL FIGURE S1. Patient flow diagram. *A multivariate approach was adopted for the purpose of adjusted analysis. Results for both acute myocardial infarction and unstable angina groups were computed using unadjusted analysis. CI = confidence interval; BP = biodegradable polymer; DES = drug-eluting stent; DOCE = device-oriented composite endpoint; HR = hazard ratio; PF = polymer free; POCE = patient-oriented composite endpoint; PP = permanent polymer.