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CLINICAL RESEARCH
Interventional cardiology

Coronary artery restenosis treatment with plain balloon, drug-coated balloon, or drug-eluting stent: 10-year outcomes of the ISAR-DESIRE 3 trial

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Abstract

Aims The best interventional strategy for the treatment of drug-eluting stent (DES) in-stent restenosis (ISR) is still unclear and no data from randomized trials beyond 3-year follow-up are available. We aimed to define 10-year comparative efficacy and safety of plain balloon (PB), paclitaxel-coated balloon (PCB), and paclitaxel-eluting stent (PES) for percutaneous coronary intervention (PCI) of DES-ISR.

Methods and results Clinical follow-up of patients randomly assigned to PB, PCB, and PES in the ISAR-DESIRE 3 trial was extended to 10 years and events were independently adjudicated. The primary endpoint was a composite of cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization. The major secondary safety endpoint was a composite of cardiac death, target vessel myocardial infarction, or target lesion thrombosis. The major secondary efficacy endpoint was target lesion revascularization. Incidences by the Kaplan–Meier method were compared by the log-rank test. Risk estimation was primarily performed by Cox proportional hazards regression and supplemented by weighted Cox regression accounting for non-proportional hazards and Royston–Parmar flexible parametric regression with a time-varying coefficient. Primary results were further assessed by landmark, lesion-level, per-protocol, and competing risk analyses. A total of 402 patients (500 lesions) with DES-ISR were randomly assigned to PB angioplasty (134 patients, 160 lesions), PCB angioplasty (137 patients, 172 lesions), and PES implantation (131 patients, 168 lesions). Clinical follow-up did not significantly differ among treatments [PB, 9.62 (4.50–10.02) years; PCB, 10.01 (5.72–10.02) years; PES, 9.08 (3.14–10.02) years; $P = 0.300$]. At 10 years, the primary composite endpoint occurred in 90 patients (72.0%) assigned to PB, 70 patients (55.9%) assigned to PCB, and 72 patients (62.4%) assigned to PES ($P < 0.001$). The pairwise comparison between PCB and PES resulted in a non-significant difference [multiplicity-adjusted $P = 0.610$; Grambsch–Therneau $P = 0.004$; weighted Cox: hazard ratio (HR) 1.10, 95% confidence interval (CI) 0.80–1.51; Cox: HR 1.10, 95% CI 0.79–1.52; Royston–Parmar: HR 1.08, 95% CI 0.72–1.60]. The major secondary safety endpoint occurred in 39 patients (34.1%) assigned to PB, 39 patients (34.0%) assigned to PCB, and 42 patients (40.0%) assigned to PES ($P = 0.564$). Target lesion revascularization occurred in 71 patients (58.0%) assigned to PB, 55 patients (43.9%) assigned to PCB, and 42 patients (38.6%)

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assigned to PES ($P < 0.0001$). The pairwise comparison between PES and PCB resulted in a non-significant difference (multiplicity-adjusted $P = 0.282$; Grambsch–Therneau $P = 0.002$; weighted Cox: HR 0.83, 95% CI 0.56–1.22; Cox: HR 0.81, 95% CI 0.54–1.21; Royston–Parmar: HR 0.75, 95% CI 0.47–1.20). Lesion-level and per-protocol analyses were consistent. At landmark analyses, an excess of death and cardiac death associated with PES compared with PCB was observed within 5 years after PCI, though 10-year differences did not formally reach the threshold of statistical significance after adjustment for multiplicity. Competing risk regression confirmed a non-significant difference in target lesion revascularization between PCB and PES and showed an increased risk of death associated with PES compared with PCB.

Conclusion Ten years after PCI for DES-ISR, the primary and major secondary endpoints between PCB and PES were not significantly different. However, an excess of death and cardiac death within 5 years associated with PES and the results of the competing risk analysis are challenging to interpret and warrant further analysis. PES and PCB significantly reduced target lesion revascularization compared with PB.

Structured Graphical Abstract

Key Question

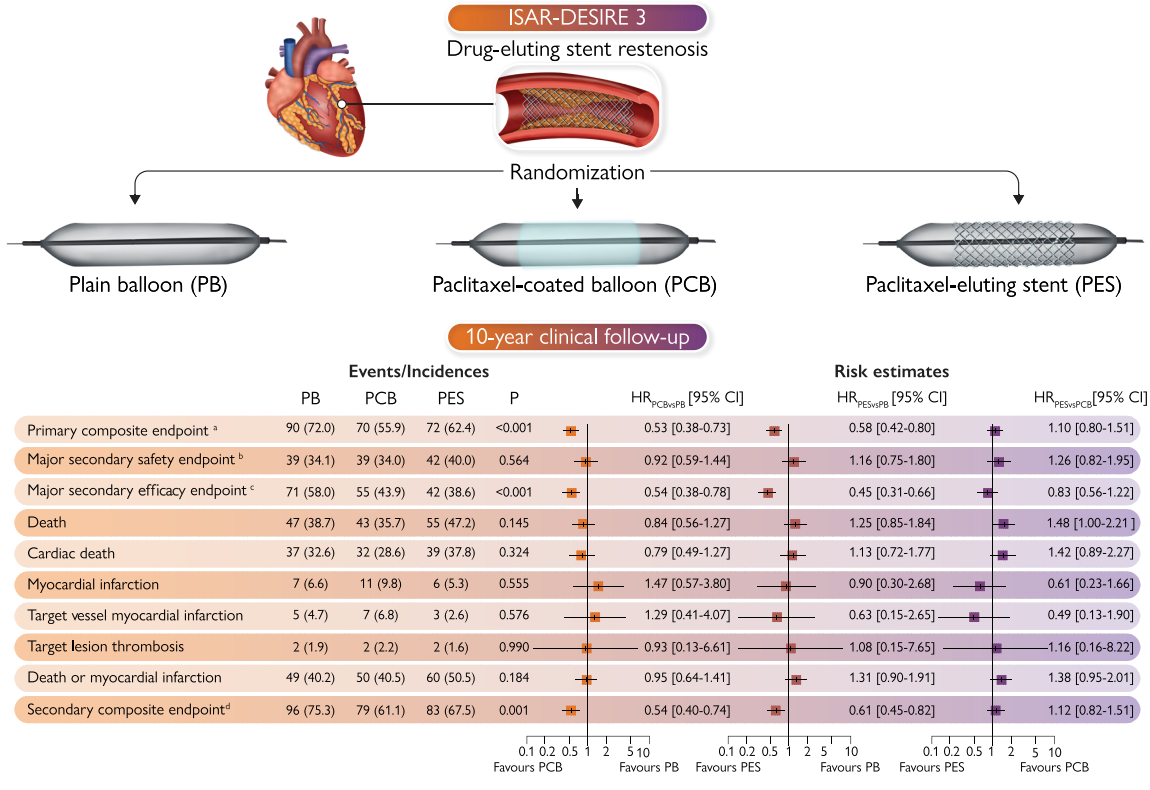
Plain balloon (PB) angioplasty, paclitaxel-coated balloon (PCB) angioplasty, and paclitaxel-eluting stent (PES) implantation are the most common treatments for drug-eluting-stent (DES) in-stent restenosis (ISR). However, comparative evidence on efficacy and safety across devices is still uncertain and available data from randomized clinical trials refer to a maximum follow-up of 3 years.

Key Finding

At 10-year follow-up, PCB angioplasty and PES implantation were associated with comparable incidences of the primary composite endpoint and target lesion revascularization and were superior to PB angioplasty for the same endpoints. Ten-year incidence of cardiac death, target vessel myocardial infarction, or target lesion thrombosis was not significantly different across groups.

Take Home Message

Differences in very late target lesion revascularization following PCB angioplasty vs. PES implantation for the treatment of DES-ISR are not significant. Both strategies are significantly more effective than PB angioplasty.



CI, confidence interval; HR, hazard ratio; PB, plain balloon; PCB, paclitaxel-coated balloon; PES, paclitaxel-eluting stent.
[a]Primary composite endpoint: Cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization.
[b]Major secondary safety endpoint: Cardiac death, target vessel myocardial infarction, or target lesion thrombosis.
[c]Major secondary efficacy endpoint: Target lesion revascularization.
[d]Secondary composite endpoint: Death, myocardial infarction, target lesion thrombosis, or target lesion revascularization. Values across treatment groups are counts and Kaplan–Meier incidences. The *P*-values refer to the *k*-sample log-rank test. Risk estimates for the primary composite endpoint, major secondary efficacy endpoint, and secondary composite endpoint are computed by weighted Cox regression accounting for non-proportional hazards. All the other risk estimates are computed by standard Cox proportional hazards regression.

Keywords Drug-coated balloon • Drug-eluting stent • In-stent restenosis • Percutaneous coronary intervention • Coronary artery disease • Long-term outcomes

Introduction

In-stent restenosis (ISR) remains a common and challenging setting of coronary artery disease.[1] Despite the introduction of highly biocompatible and performant types of drug-eluting stent (DES), the incidence of ISR in unselected patients undergoing systematic mid-term angiographic follow-up can be higher than 10%.[2] In addition, a retrospective nationwide analysis defined that among more than 5 million patients undergoing percutaneous coronary intervention (PCI) from 2009 to 2017 in the USA, more than 10% of procedures included the treatment of an ISR.[3]

PCI for the treatment of ISR has been associated with high rates of target lesion revascularization over time and in some patients with recurrent, recalcitrant ISR lesions.[4,5] There is a paucity of data related to the best treatment for ISR and this setting is often excluded from randomized trials on interventional treatments for coronary artery disease.[6,7] A comprehensive network meta-analysis of randomized trials testing available strategies for the treatment of ISR by PCI has concluded that at 6–12 months the most effective devices were drug-coated balloon (DCB) and DES;[6] the same study concluded that there were no significant differences in safety across all devices tested.[6] Another network meta-analysis of different PCI strategies for the treatment of any-type ISR has concluded that everolimus-DESs were associated with the best angiographic and clinical outcomes, followed by DCB.[7]

More recently, the DAEDALUS study, an individual patient data meta-analysis including all available randomized clinical trials comparing DCB with DES for the treatment of ISR, has shown at 3-year follow-up the superior antirestenotic efficacy of DES without significant differences in terms of individual and composite safety endpoints.[8,9] However, to date evidence from randomized clinical trials on the efficacy and safety of DCB and DES for the treatment of DES-ISR is limited to follow-up times ranging from 1 to 3 years, and it is known that some differences between interventions can require prolonged observation to emerge.[10–14]

In the present analysis, we extended clinical follow-up of patients randomly assigned to plain balloon (PB), paclitaxel-coated balloon (PCB), or paclitaxel-eluting stent (PES) for the treatment of DES-ISR in the Intracoronary Stenting and Angiographic Results - Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches (ISAR-DESIRE 3) trial to 10 years to define very late relative effectiveness and safety between these interventional strategies.[13,14]

Methods

ISAR-DESIRE 3 is a prospective, open-label, randomized clinical trial conducted at 3 German centres (Deutsches Herzzentrum München, Munich; Universitäts Herzzentrum Freiburg-Bad Krozingen, Bad Krozingen; Klinikum rechts der Isar, Munich) from August 2009 to October 2011.

The results of the primary analysis at 1-year follow-up and subsequent long-term analysis at 3-year follow-up have been previously published.[13,14]

The study was done according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices. Patients or legally authorized representatives provided written informed consent to trial participation. The analysis of data from extended follow-up was not pre-specified in the trial protocol. The approval of the 10-year clinical outcomes analysis of the ISAR-DESIRE 3 trial was issued by the Institutional Ethics Committee in September 2021. All events were adjudicated and classified by an event adjudication committee blinded to treatment allocation. The protocol was registered with ClinicalTrials.gov (NCT00987324). The trial was sponsored by the Deutsches Herzzentrum München and no extramural funding was used to accomplish the follow-up extension.

Eligibility criteria

Briefly, the trial included patients older than 18 years presenting with ischaemic symptoms or evidence of inducible or spontaneous myocardial ischaemia associated with one or more restenoses angiographically ≥50% of a limus-DES located in a native vessel. Key exclusion criteria were the following: target lesion located in the left main stem or in a coronary bypass graft, acute ST-segment elevation myocardial infarction within the preceding 48 h, cardiogenic shock, glomerular filtration rate ≤30 mL/min, malignancies, or other comorbid conditions with life expectancy <12 months or that may result in protocol non-compliance, contraindications or known allergy to antiplatelet therapy, paclitaxel, or stainless steel, and known, suspected, or planned pregnancy.

Randomization

After crossing the lesion with a guidewire, patients were randomly assigned in a 1:1:1 ratio to PB alone angioplasty, PCB angioplasty (SeQuent Please, B. Braun, Melsungen, Germany), or PES implantation (Taxus Liberté, Boston Scientific, Natick, MA, USA) by means of sealed, opaque envelopes containing a computer-generated sequence code.

Endpoints and definitions

After discharge, patients underwent systematic repeat angiography at 6–8 months and were systematically evaluated at 1 and 12 months and annually out to 10 years by phone contact or office visit in the setting of routine care. The present analysis refers to the final 10-year follow-up analysis, which is an extension of the original protocol. Original study definitions were used in this analysis to ensure a consistent clinical assessment.

The primary endpoint of the 10-year follow-up analysis was a device-oriented composite outcome including cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization. Major secondary safety and efficacy endpoints were a composite of

cardiac death, target vessel myocardial infarction, or target lesion thrombosis and the individual outcome of target lesion revascularization, respectively. Secondary individual endpoints included all-cause death, cardiac death, myocardial infarction, target vessel myocardial infarction, and target lesion thrombosis. Secondary composite endpoints included death or myocardial infarction and death, myocardial infarction, target lesion thrombosis, or target lesion revascularization.

Cardiac death was defined as death due to any of the following: acute myocardial infarction; 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 sudden or unwitnessed death in which a cardiac cause cannot be excluded. Myocardial infarction was defined on the basis of clinical symptoms, electrocardiogram, and cardiac biomarkers according to criteria used in multiple trials conducted by our research group.[15] Target vessel myocardial infarction was defined as myocardial infarction associated with electrocardiographic signs and an angiographic pattern consistent with the target vessel. Academic Research Consortium criteria for definite stent thrombosis were used for adjudication of target lesion thrombosis.[16] Target lesion revascularization was defined as any repeat revascularization procedure, percutaneous or surgical, of the target lesion.

Statistical analysis

Baseline clinical and angiographic characteristics were presented as mean and standard deviation or median and interquartile range for continuous variables and as counts and proportions for categorical variables. Differences across groups were formally tested by using the analysis of variance or Kruskal–Wallis test for continuous variables, as appropriate, and the χ^2 or Fisher exact test for categorical variables, as appropriate.

Primary analyses were conducted according to the intention-to-treat principle. Per-protocol analyses were conducted to complement primary results. Outcome incidences across groups were estimated according to the Kaplan–Meier method and compared by the log-rank test.[17] Pairwise comparisons between treatments were assessed after controlling the false discovery rate by the Benjamini–Hochberg method.[18] For each outcome, landmark analyses exploring the time periods, primarily, from index PCI to 5 years and from 5 to 10 years, and secondarily, from index PCI to 1 year and from 1 to 10 years, and from index PCI to 3 years and from 3 to 10 years, were systematically provided. Treatment-by-time period interactions were formally explored and reported for the primary and major secondary endpoints when statistically significant.

For each pairwise comparison between treatments, hazard ratio (HR) and accompanying 95% confidence interval (CI) were calculated by Cox proportional hazards regression.[17] In the eventuality of no event in a treatment group (e.g. rare outcomes such as target lesion thrombosis), computation of HR and 95% CI for the comparison of interest was performed by Cox regression with Firth's penalization.[19] The proportional hazards assumption was checked by the Grambsch–Therneau test, scaled Shoenfeld residuals, and log-minus-log plot.[17] The analyses were replicated by weighted Cox regression accounting for time-varying effects by weighting the contribution of each event time to the partial likelihood according to the product of the survivor function and the inverse cumulative probability of follow-up at that time.[20] At each event time, the weighting function is proportional to the expected number of subjects at risk if censoring has not occurred.[20] Weighted Cox regression yields estimates of average HRs independent from the proportional hazards assumption.[20] The analyses were also replicated by spline-based Royston–Parmar flexible parametric survival models with a time-varying coefficient to account for non-proportional hazards. Time-varying HRs were plotted for the primary and secondary endpoints and when there was evidence of proportional hazards violation.[21] The outcomes of target lesion revascularization, target vessel myocardial infarction, and target lesion thrombosis were also assessed at the lesion level by mixed-effects Cox models accounting for the correlation of multiple lesions per patients and treatments effect heterogeneity across patients.[22,23]

By anticipating a high incidence of death due to particularly extended follow-up with a resulting possible preclusion of the observation of the key efficacy endpoint of target lesion revascularization, a competing risks analysis with cumulative incidence function estimation and comparison by the Gray test was performed.[24] Competing risk estimates from pairwise comparisons between treatments for both competing outcomes were computed by Fine–Gray proportional subdistribution hazards regression.[25] The analyses were replicated by flexible parametric survival competing risks regression with a time-varying coefficient, consistently with the other analyses.[26]

Analyses were conducted with R 4.1.2 and STATA 14.2.

Results

A total of 402 patients (500 lesions) with DES-ISR were randomly assigned to PB angioplasty (134 patients, 160 lesions), PCB angioplasty (137 patients, 172 lesions), and PES implantation (131 patients, 168 lesions). As previously reported, baseline clinical and angiographic characteristics were balanced across treatment groups (*Table 1*). Maximum clinical follow-up did not significantly differ across treatment groups [PB, 9.62 (4.50–10.02) years; PCB, 10.01 (5.72–10.02) years; PES, 9.08 (3.14–10.02) years; $P = 0.300$].

Primary composite endpoint

At 10 years, the primary composite endpoint occurred in 90 patients (72.0%) assigned to PB, 70 patients (55.9%) assigned to PCB, and 72 patients (62.4%) assigned to PES ($P < 0.001$) (*Table 2*, *Figure 1*). The pairwise comparison between PCB and PES resulted in a non-significant difference (multiplicity-adjusted log-rank: $P = 0.610$; Grambsch–Therneau test: $P = 0.004$; weighted Cox: HR 1.10, 95% CI 0.80–1.51; Cox: HR 1.10, 95% CI 0.79–1.52; Royston–Parmar: HR 1.08, 95% CI 0.72–1.60), while both PCB and PES were superior to PB alone (multiplicity-adjusted log-rank: $P = 0.001$ and $P = 0.006$, respectively) (*Tables 2* and *3*, *Figure 1*, Supplementary material online: *Table S1*, and *Figures S1* and *S2*).

Major secondary safety and efficacy endpoints

At 10 years, cardiac death, target vessel myocardial infarction, or target lesion thrombosis occurred in 39 patients (34.1%) assigned to PB, 39 patients (34.0%) assigned to PCB, and 42 patients (40.0%) assigned to PES ($P = 0.564$) (*Table 2*, *Figure 2*). The pairwise comparison between PES and PCB resulted in a non-significant difference (multiplicity-adjusted log-rank: $P = 0.708$; weighted Cox: HR 1.29, 95% CI 0.84–1.98; Cox: HR 1.26, 95% CI 0.82–1.95; Royston–Parmar: HR 1.52, 95% CI 0.92–2.51) (*Tables 2* and *3*, *Figure 2*, Supplementary material online: *Table S1*, and *Figures S3* and *S4*). No significant differences between PCB vs. PB and PES vs. PB were observed.

At 10 years, target lesion revascularization occurred in 71 patients (58.0%) assigned to PB, 55 patients (43.9%) assigned to PCB, and 42 patients (38.6%) assigned to PES ($P < 0.0001$) (*Table 2*, *Figure 3*). The pairwise comparison between PES and PCB resulted in a non-significant difference (multiplicity-adjusted log-rank: $P = 0.282$; Grambsch–Therneau test: $P = 0.002$, weighted Cox: HR 0.83, 95% CI 0.56–1.22; Cox: HR 0.81, 95% CI 0.54–1.21; Royston–Parmar: HR 0.75, 95% CI 0.47–1.20), while both PCB and PES resulted to

Table 1 Baseline clinical and angiographic characteristics

	PB ($n = 134$)	PCB ($n = 137$)	PES ($n = 131$)
Age (years)	67.1 (9.3)	67.7 (10.4)	68.8 (10.0)
Women	39 (29)	32 (23)	43 (33)
Diabetes mellitus	50 (37)	56 (41)	61 (47)
Insulin-dependent	19 (14)	21 (15)	27 (21)
Hypertension	90 (67)	105 (77)	101 (77)
Hyperlipidaemia	102 (76)	108 (79)	103 (79)
Present smoker	22 (16)	19 (14)	15 (11)
Previous myocardial infarction	57 (43)	53 (39)	50 (38)
Prior coronary artery bypass surgery	24 (18)	15 (11)	32 (24)
Multivessel disease	127 (95)	129 (94)	122 (93)
Acute coronary syndrome	31 (23)	26 (19)	22 (17)
Left ventricular ejection fraction (%)	53.2 (9.9)	53.6 (9.8)	54.5 (9.9)
	PB ($n = 160$)	**PCB ($n = 172$)**	**PES ($n = 168$)**
Target vessel			
Left main	0	0	1 (1)
Left anterior descending	52 (33)	59 (34)	50 (30)
Left circumflex	56 (35)	54 (31)	61 (36)
Right coronary artery	52 (33)	59 (34)	56 (33)
Restenosis morphology			
Focal margin	23 (14)	31 (18)	25 (15)
Focal body	70 (44)	70 (41)	70 (42)
Multifocal	12 (8)	18 (10)	15 (9)
Diffuse	45 (28)	44 (26)	49 (29)
Proliferative	1 (1)	3 (2)	3 (2)
Occlusive	9 (6)	6 (3)	6 (4)
Index stent type			
Sirolimus-eluting	90 (56)	82 (48)	94 (56)
Everolimus-eluting	42 (26)	53 (31)	48 (29)
Zotarolimus-eluting	20 (13)	31 (18)	22 (13)
Biolimus-eluting	8 (5)	6 (3)	4 (2)
Bifurcation	37 (23)	47 (27)	40 (24)
Reference vessel diameter (mm)	2.72 (0.45)	2.75 (0.50)	2.80 (0.49)
Minimum lumen diameter (mm)	0.88 (0.49)	0.97 (0.48)	0.93 (0.50)
Diameter stenosis (%)	67.7 (15.7)	64.4 (16.8)	66.7 (16.5)

PB, plain balloon; PCB, paclitaxel-coated balloon; PES, paclitaxel-eluting stent.
Variables are reported as n (%) or mean (standard deviation). Baseline clinical characteristics are patient-level. Angiographic characteristics are lesion-level.

be significantly more effective than PB (multiplicity-adjusted log-rank: $P = 0.003$ and $P < 0.001$, respectively) (*Tables 2* and *3*, *Figure 3*, Supplementary material online: *Table S1*, and *Figures S5* and *S6*). Lesion-level analysis confirmed patient-level results (Supplementary material online: *Table S2*).

Landmark and per-protocol analyses of primary and major secondary endpoints

With respect to the primary composite endpoint, landmark analyses by 1-, 3-, and 5-year time points showed that most of the events occurred within the first years following index PCI and differences among

Table 2 Clinical outcomes

	PB ($n = 134$)	PCB ($n = 137$)	PES ($n = 131$)	P	$P_{PES\ vs.\ PCB}$	$HR_{PCB\ vs.\ PB}$ (95% CI)	$HR_{PES\ vs.\ PB}$ (95% CI)	$HR_{PES\ vs.\ PCB}$ (95% CI)
Cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization								
10 years	90 (72.0)	70 (55.9)	72 (62.4)	<0.001	0.610	0.57 (0.42–0.78)	0.63 (0.46–0.85)	1.10 (0.79–1.52)
0–5 years	74 (56.8)	53 (40.2)	51 (41.6)	<0.001	0.982	0.54 (0.38–0.76)	0.54 (0.38–0.77)	1.01 (0.69–1.48)
5–10 years	16 (35.1)	17 (26.1)	21 (35.6)	0.528	0.544	0.72 (0.37–1.43)	1.01 (0.53–1.93)	1.40 (0.74–2.65)
Cardiac death, target vessel myocardial infarction, or target lesion thrombosis								
10 years	39 (34.1)	39 (34.0)	42 (40.0)	0.564	0.708	0.92 (0.59–1.44)	1.16 (0.75–1.80)	1.26 (0.82–1.95)
0–5 years	20 (16.8)	10 (7.8)	20 (16.8)	0.071	0.064	0.47 (0.22–1.00)	1.06 (0.57–1.97)	2.27 (1.06–4.84)
5–10 years	19 (20.7)	29 (28.4)	22 (27.8)	0.524	0.747	1.39 (0.78–2.49)	1.27 (0.69–2.35)	0.91 (0.52–1.59)
Target lesion revascularization								
10 years	71 (58.0)	55 (43.9)	42 (38.6)	<0.0001	0.282	0.57 (0.40–0.81)	0.46 (0.32–0.68)	0.81 (0.54–1.21)
0–5 years	65 (50.6)	48 (36.5)	34 (29.2)	<0.0001	0.168	0.55 (0.38–0.80)	0.41 (0.27–0.62)	0.74 (0.48–1.15)
5–10 years	6 (15.1)	7 (11.5)	8 (13.3)	0.864	0.971	0.79 (0.26–2.34)	1.02 (0.35–2.93)	1.29 (0.47–3.56)
Death								
10 years	47 (38.7)	43 (35.7)	55 (47.2)	0.145	0.153	0.84 (0.56–1.27)	1.25 (0.85–1.84)	1.48 (1.00–2.21)
0–5 years	25 (20.0)	12 (9.3)	26 (20.9)	0.024	0.028	0.45 (0.23–0.90)	1.10 (0.64–1.91)	2.43 (1.23–4.82)
5–10 years	22 (23.4)	31 (29.1)	29 (33.2)	0.458	0.675	1.27 (0.74–2.20)	1.42 (0.81–2.46)	1.11 (0.67–1.85)
Cardiac death								
10 years	37 (32.6)	32 (28.6)	39 (37.8)	0.324	0.403	0.79 (0.49–1.27)	1.13 (0.72–1.77)	1.42 (0.89–2.27)
0–5 years	18 (15.2)	7 (5.8)	16 (13.6)	0.047	0.047	0.36 (0.15–0.87)	0.94 (0.48–1.85)	2.59 (1.07–6.30)
5–10 years	19 (20.5)	25 (24.3)	23 (28.0)	0.688	0.744	1.19 (0.66–2.16)	1.30 (0.71–2.39)	1.10 (0.62–1.93)
Myocardial infarction								
10 years	7 (6.6)	11 (9.8)	6 (5.3)	0.555	0.634	1.47 (0.57–3.80)	0.90 (0.30–2.68)	0.61 (0.23–1.66)
0–5 years	5 (4.3)	7 (5.3)	6 (5.3)	0.881	0.906	1.33 (0.42–4.19)	1.25 (0.38–4.10)	0.94 (0.32–2.80)
5–10 years	2 (2.3)	4 (4.7)	0	0.193	0.210	1.61 (0.29–9.08)[a]	0.22 (0.01–6.44)[a]	0.13 (0.01–3.52)[a]
Target vessel myocardial infarction								
10 years	5 (4.7)	7 (6.8)	3 (2.6)	0.576	0.661	1.29 (0.41–4.07)	0.63 (0.15–2.65)	0.49 (0.13–1.90)
0–5 years	4 (3.6)	3 (2.3)	3 (2.6)	0.891	0.904	0.70 (0.16–3.14)	0.79 (0.18–3.51)	1.12 (0.23–5.54)
5–10 years	1 (1.1)	4 (4.7)	0	0.115	0.207	2.68 (0.33–22.04)[a]	0.36 (0.01–13.80)[a]	0.13 (0.00–3.75)[a]
Target lesion thrombosis								
10 years	2 (1.9)	2 (2.2)	2 (1.6)	0.990	0.943	0.93 (0.13–6.61)	1.08 (0.15–7.65)	1.16 (0.16–8.22)
0–5 years	2 (1.9)	1 (0.7)	2 (1.6)	0.776	0.796	0.48 (0.04–5.25)	1.06 (0.15–7.54)	2.23 (0.20–24.63)
5–10 years	0	1 (1.4)	0	0.457	0.592	2.52 (0.02–397.64)[a]	–	0.46 (0.00–72.54)[a]
Death or myocardial infarction								
10 years	49 (40.2)	50 (40.5)	60 (50.5)	0.184	0.238	0.95 (0.64–1.41)	1.31 (0.90–1.91)	1.38 (0.95–2.01)
0–5 years	28 (22.4)	18 (13.6)	32 (25.5)	0.062	0.060	0.61 (0.34–1.10)	1.21 (0.73–2.00)	1.97 (1.11–3.52)
5–10 years	21 (23.0)	32 (31.1)	28 (33.5)	0.385	0.868	1.39 (0.80–2.40)	1.45 (0.82–2.54)	1.04 (0.63–1.73)
Death, myocardial infarction, target lesion thrombosis, or target lesion revascularization								
10 years	96 (75.3)	79 (61.1)	83 (67.5)	0.001	0.489	0.60 (0.44–0.81)	0.67 (0.50–0.90)	1.12 (0.82–1.53)

Continued

Table 2 *Continued*

	PB ($n = 134$)	PCB ($n = 137$)	PES ($n = 131$)	*P*	$P_{PES\ vs.\ PCB}$	$HR_{PCB\ vs.\ PB}$ (95% CI)	$HR_{PES\ vs.\ PB}$ (95% CI)	$HR_{PES\ vs.\ PCB}$ (95% CI)
0–5 years	78 (59.5)	57 (42.7)	59 (46.5)	<0.001	0.708	0.55 (0.39–0.77)	0.59 (0.42–0.83)	1.09 (0.75–1.56)
5–10 years	18 (39.0)	22 (32.1)	24 (39.3)	0.735	0.800	0.82 (0.44–1.52)	1.01 (0.55–1.85)	1.23 (0.69–2.20)

CI, confidence interval; HR, hazard ratio; *P*, log-rank test *P*-value; $P_{PES\ vs.\ PCB}$, log-rank test *P*-value for the comparison PES vs. PCB adjusted for multiplicity; PB, plain balloon; PCB, paclitaxel-coated balloon; PES, paclitaxel-eluting stent.
The table illustrates main clinical outcomes at 10-year follow-up and within the time periods from PCI for the treatment of ISR to 5 years and from 5 to 10 years. Analyses are conducted according to the intention-to-treat principle.
Left: Number of events and corresponding Kaplan–Meier incidences across treatment groups. Asymptotic three-group log-rank test and multiplicity-adjusted log-rank test for the comparison of PES vs. PCB are provided.
Right: Cox proportional hazards regression models for the pairwise comparisons between PB, PCB, and PES.
[a]Cox regression with Firth's penalized likelihood.

treatments were highly significant in these periods (1 year: $P < 0.0001$; 3 years: $P < 0.0001$; 5 years: $P < 0.001$), while no significant differences were observed in subsequent periods up to 10 years (1–10 years: $P = 0.405$; 3–10 years: $P = 0.344$; 5–10 years: $P = 0.528$) (*Tables 2* and *3*, *Figure 4A*, Supplementary material online: *Tables S1* and *S3–S8*, and *Figure S2*). Incidences from 1, 3, and 5 to 10 years continued to steadily increase and, although the PES group tended to be associated with a numerical excess of events within these time periods, no significant differences among treatment groups were observed and no treatment-by-time period interaction between PCB and PES was detected (*Tables 2* and *3*, *Figure 4A*, Supplementary material online: *Tables S1* and *S3–S8*, and *Figure S2*). Per-protocol analyses showed results consistent with those of intention-to-treat analyses, with confirmation of the superiority of PCB and PES over PB and the absence of significant differences between PES and PCB at 10-year follow-up (Grambsch–Therneau test: $P = 0.008$; weighted Cox: HR 1.15, 95% CI 0.83–1.59; Cox: HR 1.15, 95% CI 0.82–1.61; Royston–Parmar: HR 1.11, 95% CI 0.74–1.67), after exclusion of protocol deviations and treatment crossover (Supplementary material online: *Tables S9–S11*).

With respect to the major secondary safety endpoint of cardiac death, target vessel myocardial infarction, or target lesion thrombosis, the occurrence of events across treatments did not show significant differences within time periods, except for an increased risk from PCI for the treatment of DES-ISR to 5 years associated with PES compared with PCB (*Tables 2* and *3*, *Figure 4B*, Supplementary material online: *Tables S1* and *S3–S8*, and *Figure S4*); however, the *P*-value of interaction testing was formally non-significant ($P = 0.058$) (*Figure 4B*). Per-protocol analyses confirmed the absence of significant differences across treatments at 10-year follow-up (PES vs. PCB: Cox: HR 1.28, 95% CI 0.82–1.99; weighted Cox: HR 1.30, 95% CI 0.84–2.01; Royston–Parmar: HR 1.60, 95% CI 0.96–2.67) (*Table 3*, Supplementary material online: *Tables S9-S11*).

With respect to the major secondary efficacy endpoint of target lesion revascularization, the occurrence of events was higher in the first years following index PCI and differences among treatments were highly significant during these time periods ($P < 0.0001$) due to a significantly higher antirestenotic efficacy of PCB and PES compared with PB (*Tables 2* and *3*, *Figure 4C*, Supplementary material online: *Tables S1* and *S3–S8*, and *Figure S6*). A numerical advantage of PES over PCB at 1, 3, and 5 years was progressively mitigated with limited differences in the incidence of target lesion revascularization between treatment groups in subsequent time periods (*Table 2*, *Figure 4C*, Supplementary material online: *Tables S1*, *S2* and *S4–S9*, and *Figure S6*). Although treatment-by-time period interaction *P*-values between 0–1 year and 1–10 years periods for PCB vs. PB and PES vs. PB were significant, there was no significant interaction for PES vs. PCB. Per-protocol analyses were consistent with intention-to-treat analyses, with confirmation of the superior effectiveness of PCB and PES over PB and the non-significant difference between PES and PCB (Grambsch–Therneau test: $P = 0.005$; weighted Cox: HR 0.86, 95% CI 0.58–1.27; Cox: HR 0.84, 95% CI 0.56–1.26; Royston–Parmar: HR 0.77, 95% CI 0.48–1.24) (Supplementary material online: *Tables S9–S11*).

Secondary endpoints

Over 10 years following index PCI, there was a significant excess in the risk of all-cause death in patients assigned to PES compared with those assigned to PCB (55 patients, 47.2% vs. 43 patients, 35.7%; Cox: HR 1.48, 95% CI 1.00–2.21; weighted Cox: HR 1.54, 95% CI 1.04–2.28; Royston–Parmar: HR 2.05, 95% CI 1.16–3.63) (*Tables 2* and *3*, Supplementary material online: *Table S1* and *Figure S7*). However, the difference adjusted for multiplicity was not significant ($P = 0.153$). At landmark analyses, a significant excess (multiplicity-adjusted *P*-value = 0.028; Cox: HR 2.43, 95% CI 1.23–4.82; weighted Cox: HR 2.47, 95% 1.24–4.89; Royston–Parmar: HR 3.22, 95% CI 1.46–7.08) of mortality associated with PES compared with PCB was mainly observed within 5 years, while no significant differences among treatments were observed from 5 to 10 years (*Tables 2* and *3*, Supplementary material online: *Table S1* and *Figure S7*); however, treatment-by-time period interaction for PCB vs. PES was formally non-significant ($P = 0.072$) (Supplementary material online: *Figure S7*). Per-protocol analyses by weighted Cox regression and flexible parametric Royston–Parmar models confirmed a significant risk increase associated with PES compared with PCB (Supplementary material online: *Tables S10 and S11*). A consistent, significant increase in cardiac death within 5 years was associated with PES compared with PCB (multiplicity-adjusted $P = 0.047$; Cox: HR 2.59, 95% CI 1.07–6.30; weighted Cox: HR 2.55, 95% CI 1.05–6.19; Royston–Parmar: HR 3.00, 95% CI 1.18–7.65) (*Tables 2* and *3*, Supplementary material online: *Table S1 and Figure S8*), while no differences among treatments were observed from 5 to 10 years; however, treatment-by-time period interaction for PCB vs. PES was not statistically significant ($P = 0.110$) (Supplementary material online: *Figure S8*). Ten-year death and cardiac death incidences between PCB vs. PB and PES vs. PB were not significantly different (*Tables 2* and *3*, Supplementary material online: *Table S1* and *Figure S8*). The other landmark analyses and per-protocol analyses were consistent (Supplementary material online: *Tables S3–S11*).

Over 10 years following index PCI, differences in the individual endpoints of myocardial infarction, target vessel myocardial infarction, and

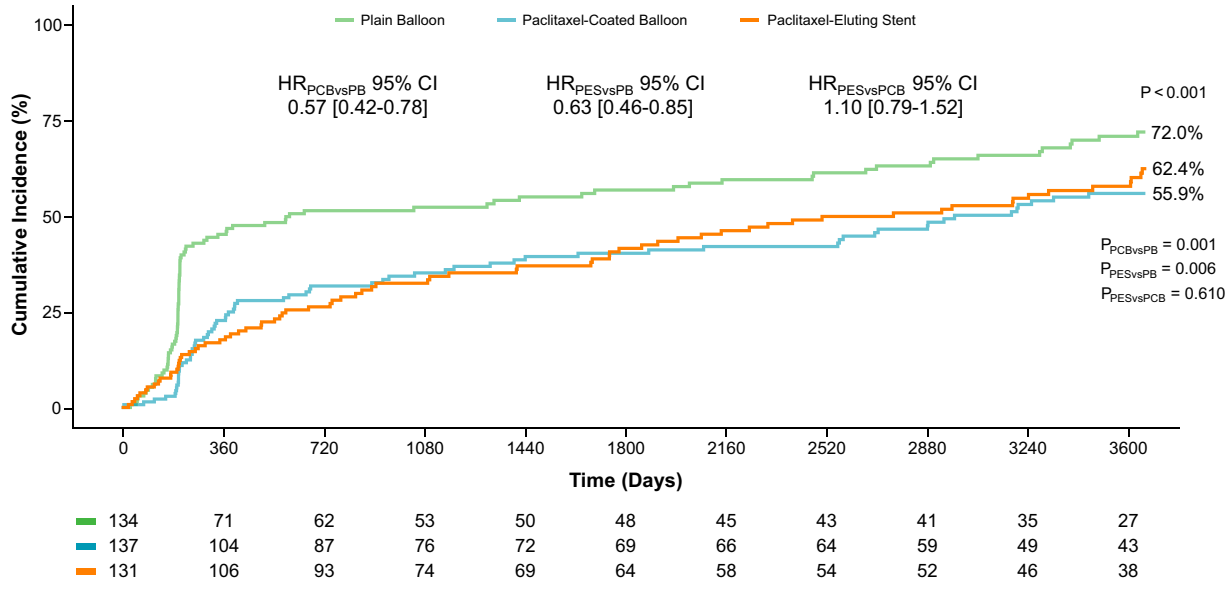


Figure 1 Device-oriented primary composite endpoint. CI, confidence interval; HR, hazard ratio; *P*, *k*-sample log-rank test; $P_{PESvsPCB}$/$P_{PESvsPCB}$/$P_{PESvsPCB}$, multiplicity-adjusted log-rank test for each pairwise comparison; PB, plain balloon; PCB, paclitaxel-coated balloon; PES, paclitaxel-eluting stent. The device-oriented primary composite endpoint included cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization. Incidences are estimated by the Kaplan–Meier method and compared by the log-rank test. Multiplicity-adjusted log-rank test *P*-values (Benjamini–Hochberg) of pairwise comparisons are supplemented due to the *k*-sample log-rank test significance. HRs and 95% CIs by Cox proportional hazards regression are reported for each pairwise comparison.

target lesion thrombosis were not significantly different among treatments (*Tables 2* and *3*, Supplementary material online: *Table S1*, and *Figures S9* and *S10*). Landmark and per-protocol analyses showed consistent conclusions (*Tables 2* and *3*, Supplementary material online: *Tables S1* and *S3–S11*). Lesion-level analyses of target vessel myocardial infarction and target lesion thrombosis were consistent with patient-level analyses (Supplementary material online: *Table S2*).

The composite endpoint of death or myocardial infarction was not significantly different among treatments by conventional analysis and weighted Cox regression, while time-varying coefficient flexible parametric regression models resulted in a significant risk increase associated with PES compared with PCB (*Tables 2* and *3*, Supplementary material online: *Tables S1*). PCB and PES were associated with lower 10-year incidences of death, myocardial infarction, target lesion thrombosis, or target lesion revascularization compared with PB, essentially as a result of their higher antirestenotic efficacy (*Tables 2* and *3*, Supplementary material online: *Table S1*). No significant differences between PCB and PES in 10-year death, myocardial infarction, target lesion thrombosis, or target lesion revascularization were observed (multiplicity-adjusted *P*-value: 0.489; weighted Cox: HR 1.12, 95% CI 0.82–1.51; Cox: HR 1.12, 95% CI 0.82–1.53; Royston–Parmar: HR 1.28, 95% CI 0.88–1.87) (*Tables 2* and *3*, Supplementary material online: *Table S1*). Landmark analyses showed an excess in the risk of death or myocardial infarction within the first 5 years associated with PES compared with PCB, but treatment-by-time period interaction was not statistically significant ($P = 0.104$) (*Tables 2* and *3*, Supplementary material online: *Tables S1* and *S3–S8*, and *Figures S9* and *S10*). The analysis of time-varying coefficient HRs for death, myocardial infarction, target lesion thrombosis, or target lesion revascularization confirmed that differences in treatment effects emerged early and remained relatively stable for the first period (Supplementary material online: *Figure S11*). Per-protocol analyses showed consistent conclusions (Supplementary material online: *Tables S9–S11*).

Competing risks analysis

The comparison of cumulative incidence functions by treatment group resulted in significant differences for both target lesion revascularization and death (*Figure 5*). PES implantation was associated with the lowest and highest values in terms of target lesion revascularization and death, respectively. Competing risks regression for the comparison between PES implantation and PCB angioplasty confirmed a non-significant difference in target lesion revascularization (Fine–Gray: HR 0.74, 95% CI 0.50–1.11). In patients who died without preceding target lesion revascularization, subdistribution hazards regression informed of a significant mortality risk increase associated with PES compared with PCB (Fine–Gray: HR 1.99, 95% CI 1.18–3.34). Results by flexible parametric regression with a time-varying coefficient were consistent (target lesion revascularization: HR 0.69, 95% CI 0.45–1.04; death: HR 1.85, 95% CI 1.01–3.38) (Supplementary material online: *Table S12*).

Discussion

The main findings of the 10-year follow-up analysis of the ISAR-DESIRE 3 trial are the following (*Structured Graphical Abstract*):

- PCB angioplasty and PES implantation are associated with comparable 10-year incidences of a device-oriented composite endpoint including cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization;

Table 3 Ten-year clinical outcomes and landmark analysis from PCI for DES-ISR to 5 years and from 5 to 10 years by weighted Cox regression accounting for non-proportional hazards

	P_{GT}	$HR_{PCB\ vs.\ PB}$ (95% CI)	$HR_{PES\ vs.\ PB}$ (95% CI)	$HR_{PES\ vs.\ PCB}$ (95% CI)
Cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization				
10 years	0.004	0.53 (0.38–0.73)	0.58 (0.42–0.80)	1.10 (0.80–1.51)
0–5 years	0.003	0.50 (0.35–0.71)	0.51 (0.36–0.74)	1.03 (0.70–1.49)
5–10 years	0.942	0.72 (0.37–1.42)	1.02 (0.54–1.95)	1.42 (0.75–2.69)
Cardiac death, target vessel myocardial infarction, or target lesion thrombosis				
10 years	0.127	0.89 (0.57–1.38)	1.14 (0.74–1.78)	1.29 (0.84–1.98)
0–5 years	0.518	0.45 (0.21–0.96)	1.03 (0.56–1.91)	2.29 (1.07–4.89)
5–10 years	0.218	1.38 (0.77–2.48)	1.27 (0.69–2.34)	0.92 (0.53–1.58)
Target lesion revascularization				
10 years	0.002	0.54 (0.38–0.78)	0.45 (0.31–0.66)	0.83 (0.56–1.22)
0–5 years	0.001	0.52 (0.36–0.76)	0.40 (0.26–0.61)	0.76 (0.50–1.17)
5–10 years	0.084	0.76 (0.26–2.21)	0.96 (0.33–2.75)	1.26 (0.46–3.49)
Death				
10 years	0.132	0.80 (0.53–1.21)	1.23 (0.83–1.83)	1.54 (1.04–2.28)
0–5 years	0.393	0.45 (0.23–0.89)	1.10 (0.64–1.91)	2.47 (1.24–4.89)
5–10 years	0.493	1.26 (0.73–2.18)	1.40 (0.81–2.44)	1.11 (0.67–1.84)
Cardiac death				
10 years	0.154	0.77 (0.48–1.24)	1.11 (0.71–1.75)	1.44 (0.91–2.27)
0–5 years	0.314	0.36 (0.15–0.86)	0.92 (0.47–1.81)	2.55 (1.05–6.19)
5–10 years	0.224	1.18 (0.65–2.16)	1.30 (0.71–2.39)	1.10 (0.63–1.93)
Myocardial infarction				
10 years	0.583	1.51 (0.58–3.92)	0.83 (0.28–2.47)	0.55 (0.20–1.49)
0–5 years	0.757	1.23 (0.39–3.89)	1.22 (0.37–3.96)	0.99 (0.33–2.95)
5–10 years	0.322	2.04 (0.37–11.15)	–	–
Target vessel myocardial infarction				
10 years	0.223	1.45 (0.46–4.62)	0.58 (0.14–2.45)	0.40 (0.10–1.56)
0–5 years	0.679	0.62 (0.14–2.78)	0.74 (0.17–3.27)	1.19 (0.24–5.95)
5–10 years	0.300	4.23 (0.47–38.18)	–	–
Target lesion thrombosis				
10 years	0.539	1.15 (0.16–8.45)	0.89 (0.13–6.25)	0.77 (0.11–5.49)
0-5 years	0.107	0.37 (0.03–4.17)	0.87 (0.12–6.02)	2.32 (0.21–26.11)
5–10 years	–	–	–	–
Death or myocardial infarction				
10 years	0.241	0.90 (0.61–1.34)	1.29 (0.88–1.89)	1.43 (0.99–2.08)
0–5 years	0.513	0.61 (0.34–1.09)	1.21 (0.73–1.99)	1.99 (1.11–3.55)
5–10 years	0.385	1.36 (0.78–2.37)	1.42 (0.81–2.51)	1.05 (0.63–1.73)
Death, myocardial infarction, target lesion thrombosis, or target lesion revascularization				
10 years	0.005	0.54 (0.40–0.74)	0.61 (0.45–0.82)	1.12 (0.82–1.51)

Continued

Table 3 *Continued*

	P_{GT}	$HR_{PCB\ vs.\ PB}$ (95% CI)	$HR_{PES\ vs.\ PB}$ (95% CI)	$HR_{PES\ vs.\ PCB}$ (95% CI)
0–5 years	0.003	0.50 (0.36–0.71)	0.55 (0.39–0.78)	1.09 (0.76–1.55)
5–10 years	0.852	0.82 (0.44–1.53)	1.02 (0.56–1.88)	1.24 (0.69–2.22)

CI, confidence interval; HR, hazard ratio; PB, plain balloon; P_{GT}, *P*-value of the Grambsch–Therneau test; PCB, paclitaxel-coated balloon; PES, paclitaxel-eluting stent.
The table illustrates main clinical outcomes at 10-year follow-up and within the time periods from PCI for the treatment of DES-ISR to 5 years and from 5 to 10 years by weighted Cox regression allowing the estimation of unbiased average HRs when the proportional hazards assumption is violated. A significant Grambsch–Therneau test *P*-value formally indicates that the proportional hazards assumption is violated. Formal testing was supplemented by visual inspection of scaled Schoenfeld residuals and log-minus-log plot. Analyses are conducted according to the intention-to-treat principle.

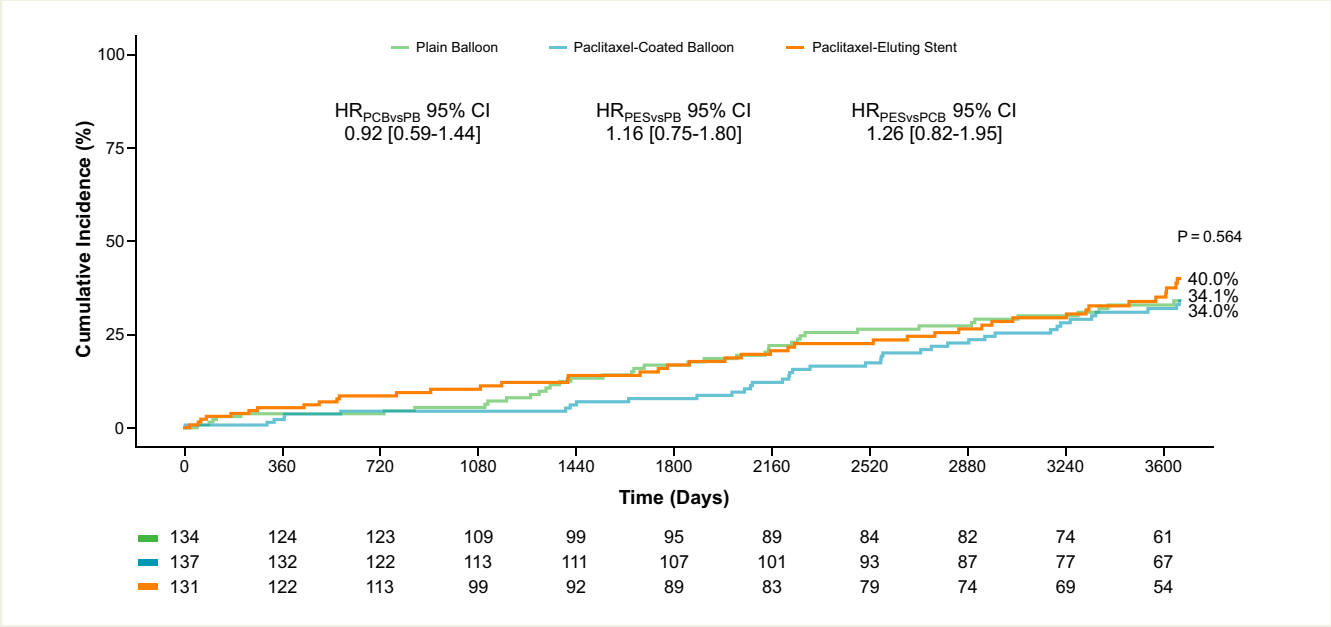


Figure 2 Cardiac death, target vessel myocardial infarction, or target lesion thrombosis. CI, confidence interval; HR, hazard ratio; *P*, *k*-sample log-rank test; PB, plain balloon; PCB, paclitaxel-coated balloon; PES, paclitaxel-eluting stent. Incidences of the major secondary endpoint of cardiac death, target vessel myocardial infarction, or target lesion thrombosis are estimated by the Kaplan–Meier method and compared by the log-rank test. HRs and 95% CIs by Cox proportional hazards regression are reported for each pairwise comparison.

- DES-ISR is an extremely challenging pattern of coronary artery disease characterized by 10-year incidences of recurrent target lesion revascularization ranging from 38.6% to 58.0% depending on the interventional strategy used;
- at 10 years, the incidence of target lesion revascularization between PCB angioplasty and repeat PES implantation is not significantly different and an early numerical advantage associated with PES progressively weakens over time, with an occurrence of events comparable to PCB after the first years following index PCI;
- at 10 years, PCB angioplasty and PES implantation significantly reduce the incidence of repeat target lesion revascularization compared with PB angioplasty alone;
- at 10 years, the incidence of cardiac death, target vessel myocardial infarction, or target lesion thrombosis is not significantly different among treatments, though a numerical excess of death and cardiac death, especially within the first 5 years, warrants further analysis; and
- a competing risk analysis does not indicate a significant influence of death on 10-year target lesion revascularization, but it also shows an increased risk of death after PES implantation compared with PCB angioplasty which is challenging to interpret and requires further data.

To date, there is no information on very late outcomes following PCI for the treatment of DES-ISR.[27,28] Available randomized clinical trials on treatments for DES-ISR have maximum available follow-up ranging from 1 to 3 years.[6–8,29] To the best of our knowledge, no *post hoc* extension of final 2- or 3-year follow-up has been planned for the few trials that can have reached 10 years since the enrolment of the last patients.[6–8,29] In addition, several years would be required before patients enrolled in more recent trials can achieve very late follow-up.[6–8,29]

The 10-year follow-up analysis of the ISAR-DESIRE 3 trial represents the first analysis of a randomized clinical trial on the treatment of DES-ISR reporting outcomes of PB angioplasty alone, PCB angioplasty, or PES implantation beyond 3 years after index PCI. The study concludes that at 10 years PCB angioplasty and PES implantation significantly reduce the incidence of a device-oriented composite endpoint including cardiac death, target vessel myocardial infarction, target lesion

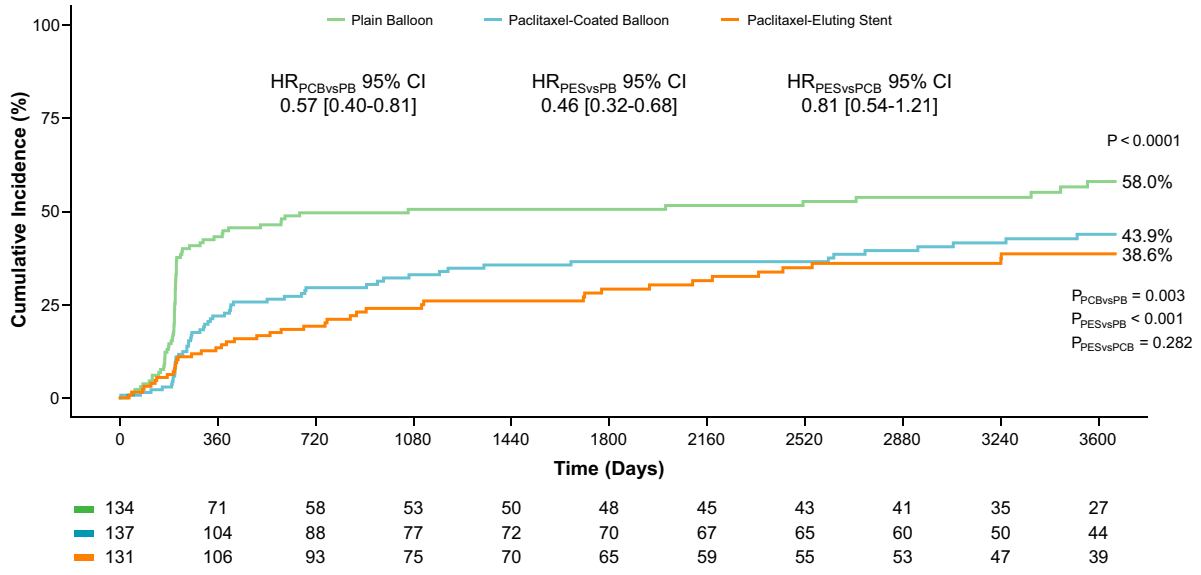


Figure 3 Target lesion revascularization. CI, confidence interval; HR, hazard ratio; *P*, *k*-sample log-rank test; $P_{PESvsPCB}/P_{PESvsPCB}/P_{PESvsPCB}$, multiplicity-adjusted log-rank test for each pairwise comparison; PB, plain balloon; PCB, paclitaxel-coated balloon; PES, paclitaxel-eluting stent. Incidences of the major efficacy secondary endpoint of target lesion revascularization are estimated by the Kaplan–Meier method and compared by the log-rank test. Multiplicity-adjusted log-rank test *P*-values (Benjamini–Hochberg) of pairwise comparisons are supplemented due to the *k*-sample log-rank test significance. HRs and 95% CIs by Cox proportional hazards regression are reported for each pairwise comparison.

thrombosis, or target lesion revascularization compared with PB angioplasty alone and no significant very late difference between PCB and PES is observed.

In the present analysis, the 10-year incidence of target lesion revascularization following PB angioplasty was unacceptably higher than following PCB angioplasty and PES implantation. By considering the similar 10-year incidences of composite and individual safety endpoints between PB and PCB, the preferential, systematic use of DCB over PB for the treatment of DES-ISR should be pursued in those cases in which repeat stenting with DES is not preferred. In contemporary PCI, the reasons for adopting a PB alone strategy for ISR instead of DCB or DES are very limited.

The results of the ISAR-DESIRE 3 trial support the use of the drug-based devices in patients with DES-ISR, but the disadvantage of an additional permanent metallic layer of repeat stenting with DES should be weighed case by case for the potential risk of reiteration of the mechanisms leading to ISR.

More in general, the decision between DCB and DES for the treatment of ISR should account at the same time for multiple relevant factors including the lesion pattern at angiography (i.e. focal margin or gap, focal body, diffuse, proliferative, occlusive) and endovascular imaging (i.e. heterogeneous tissue, layered structure, homogenous tissue, calcified nodule, thin-cap neoatherosclerotic fibroatheroma, etc.), predominant mechanism of failure (i.e. neointimal hyperplasia, neoatherosclerosis, stent underexpansion/undersizing, stent fracture, etc.), lesion presentation (i.e. first or recurrent ISR), previous treatments and metallic layers (in the case of recurrent ISR), type of restenotic stent (i.e. bare-metal stent or DES), associations with clinical presentation (i.e. ISR as the culprit or secondary lesion, stable or unstable ISR), lesion length and location (i.e. left main, bifurcation, chronic total occlusion, etc.), reference vessel diameter (e.g. ISR in small vessels), and individual patient risk profile in relation to ISR recurrence (e.g. diabetes, chronic kidney disease, etc.).[27,28]

Although in many of these conditions, DCB angioplasty and DES implantation can be similarly effective and safe, in the decision of the interventional strategy for ISR lesions amenable to treatment with DCB angioplasty and DES implantation, it is reasonable to consider that DCB angioplasty does not preclude the subsequent revascularization by DES implantation in the case of recurrent restenosis. The results of the ISAR-DESIRE 3 trial indicate that treatment with PCB is not associated with safety issues in terms of composite and individual ischaemic endpoints, while there is residual uncertainty surrounding the comparative long-term safety of PES implantation for DES-ISR.

The 10-year outcome analysis of the ISAR-DESIRE 3 trial also supports the conclusion that DES-ISR treatment is associated with worse rates of target lesion revascularization compared with *de novo* disease. Indeed, in the present study, 10-year incidences of target lesion revascularization in patients assigned to PCB and PES were 43.9% and 38.6%, respectively. In the 10-year follow-up analyses of the ISAR-TEST 4 and ISAR-TEST 5 trials, including patients with *de novo* coronary artery disease, rates of target lesion revascularization among different DESs were substantially lower, ranging from 18.2% to 22.5% in the first trial and from 20.6% to 21.9% in the second trial.[30,31]

Known complex histopathology features of DES-ISR, including proteoglycan-rich neointimal hyperplasia with relatively few muscle cells, accelerated neoatherosclerotic changes, layered heterogeneous tissue composition, and late thin-cap fibroatheroma and lipid-rich neointima formation, can partially explain the higher rates of target lesion revascularization compared with *de novo* coronary artery disease.[32,33]

Additional explanations may be provided by differences in clinical characteristics between patients with ISR and *de novo* coronary artery disease. Prior data have indicated that patients undergoing PCI for ISR more likely suffer from conditions associated with target lesion failure, such as diabetes, complex coronary artery disease, multivessel disease,

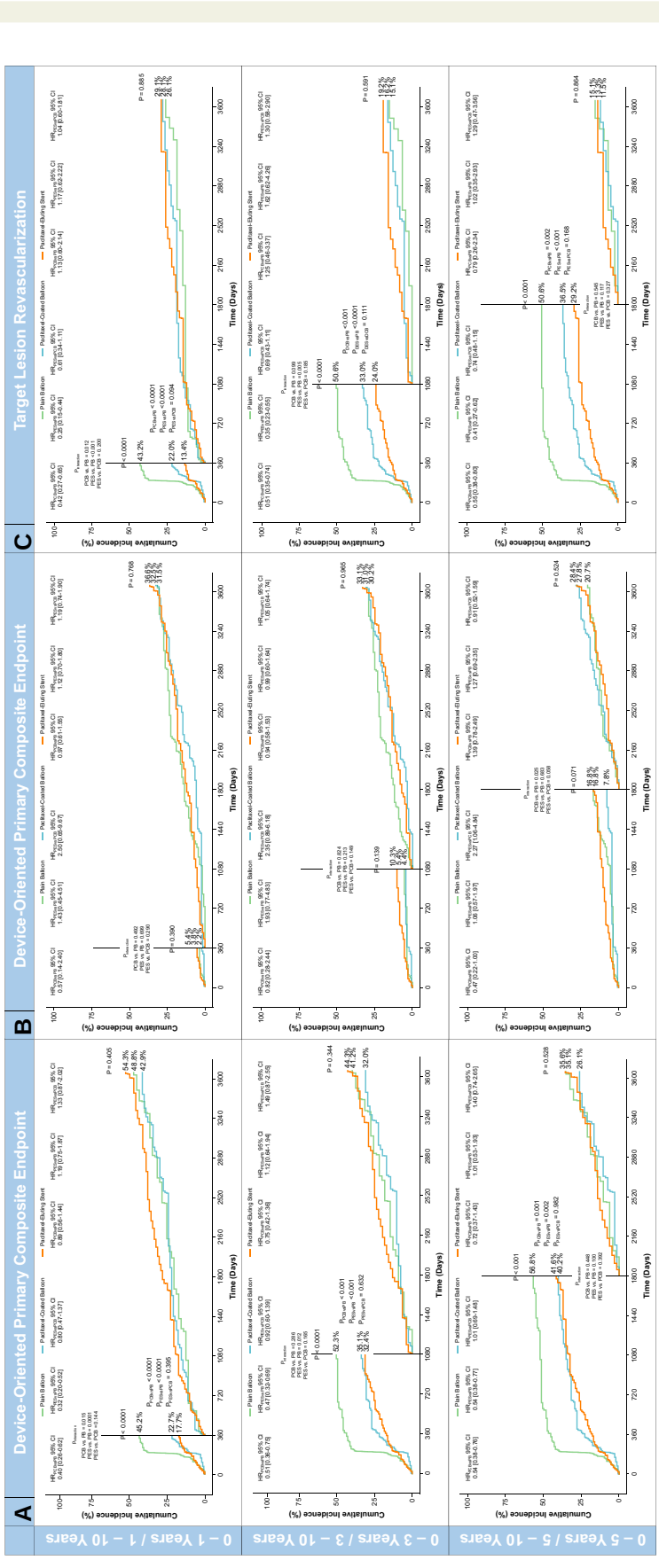
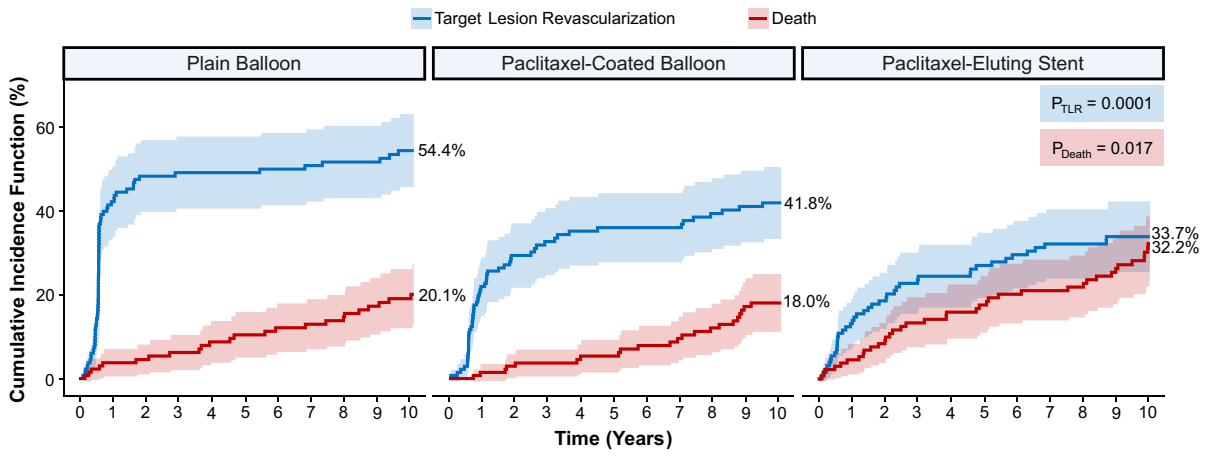


Figure 4 Landmark analyses. CI, confidence interval; HR, hazard ratio; *P*, *k*-sample log-rank test; $P_{PES vs PCB}$/$P_{PES vs PCB}$/$P_{PES vs PCB}$, multiplicity-adjusted log-rank test for each pairwise comparison; $P_{interaction}$, *P*-values of interaction testing by time periods; PB, plain balloon; PCB, paclitaxel-coated balloon; PES, paclitaxel-eluting stent. The device-oriented primary composite endpoint of cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization (*A*), major secondary safety endpoint of cardiac death, target vessel myocardial infarction, or target lesion thrombosis (*B*), and major secondary efficacy endpoint of target lesion revascularization (*C*) by the landmark time points of 1, 3, and 5 years following index PCI (upper, central, and lower row, respectively). Incidences are estimated by the Kaplan–Meier method (solid lines) and compared by the log-rank test. Multiplicity-adjusted log-rank test *P*-values (Benjamini–Hochberg) of pairwise comparisons are supplemented when the *k*-sample log-rank test indicates a significant three-group difference. HRs and 95% CIs by Cox proportional hazards regression are reported for each pairwise comparison.



Fine-Gray Competing Risk Model	Target Lesion Revascularization HR [95% CI]	Death HR [95% CI]
Paclitaxel-Coated Balloon vs. Plain Balloon	0.60 [0.42-0.85]	0.87 [0.49-1.54]
Paclitaxel-Eluting Stent vs. Plain Balloon	0.68 [0.57-0.83]	1.31 [1.02-1.69]
Paclitaxel-Eluting Stent vs. Paclitaxel-Coated Balloon	0.74 [0.50-1.11]	1.99 [1.18-3.34]

Figure 5 Competing risk analysis. CI, confidence interval; HR, hazard ratio; P_{Death}, *P* value of the comparison between cumulative incidence functions of death; P_{TLR}, *P* value of the comparison between cumulative incidence functions of target lesion revascularization. Cumulative incidence functions of target lesion revascularization and death by treatment with PB, PCB, and PES are illustrated. Differences in cumulative incidence functions by treatment group in terms of target lesion revascularization (P_{TLR}) and death (P_{Death}) were significant. For each pairwise comparison, estimated subdistribution HRs and 95% CIs for target lesion revascularization and death were estimated by Fine–Gray models.

and prior repeat revascularization, when compared with patients undergoing PCI for *de novo* coronary artery disease.[2]

The DAEDALUS study has recently shown in 1976 patients undergoing PCI for ISR in 10 randomized clinical trials that repeat DES implantation is more effective than DCB angioplasty in reducing the 3-year incidence of target lesion revascularization.[8] In another analysis from the same study, the different performance of the two devices seemed to be more pronounced in the DES-ISR setting, where repeat DES implantation reduced by 37% the risk of target lesion revascularization compared with DCB angioplasty.[9]

In the present analysis, at 10-year follow-up, we did not observe statistically significant differences between PCB and PES and an early numerical advantage of PES implantation faded over time, with comparable occurrence of target lesion revascularization in the two treatment groups after 1, 3, and 5 years from index PCI. These findings may indicate that vessel scaffolding due to repeat DES implantation produces an improved angiographic appearance at follow-up and a non-significant trend towards lower target lesion revascularization within the first years after index PCI, followed by the subsequent mitigation of this effect over time. However, although some trials on DCB vs. DES for DES-ISR reported superior mid-term angiographic outcomes associated with repeat DES implantation,[6,7] this conclusion was not consistently reported across available data and in the primary analysis of the ISAR-DESIRE 3 trials, 6–8 month angiography follow-up showed that PCB was non-inferior to PES in terms of percentage diameter stenosis (38.0% ± 21.5 vs. 37.4% ± 21.8; $P_{noninferiority} = 0.007$, one-sided 95% CI 4.9%, non-inferiority margin of 7%).[13]

The DAEDALUS study also informed of a non-significant excess of 3-year death, myocardial infarction, or target lesion thrombosis associated with DES implantation compared with DCB angioplasty.[8] The present 10-year analysis of the ISAR-DESIRE 3 trial partially supports this finding. On the one hand, at 10 years the incidence of cardiac death, target vessel myocardial infarction, or target lesion thrombosis was not significantly different among treatment groups. On the other hand, in the first years following index PCI, an excess of death and cardiac death was noticed in patients assigned to PES compared with patients assigned to PCB. The interpretation of these findings is challenging since it may be a play of chance but also an expression of repeat DES implantation late unsafety. Unaddressed questions on death and cardiac death following repeat DES implantation for DES-ISR require larger analyses with very long-term follow-up.

Of note, in the present analysis, PCB was not associated with increased long-term mortality. This finding is relevant in consideration of late safety concerns related to PCB use in peripheral artery disease.[34] Indeed, although it has been clearly demonstrated that PCB angioplasty for femoropopliteal artery disease is significantly more effective than PB, in both *de novo* and ISR settings,[35–37] a recent meta-analysis has raised concerns related to the late safety of PCB angioplasty due to the observation of reduced long-term survival in patients receiving this treatment.[34] This finding was initially adduced to a possible paclitaxel-related toxicity.[34] In contrast, in the present analysis of the ISAR-DESIRE 3 trial, we show a favourable 10-year survival incidence in patients assigned to PCB and the difference in 10-year mortality between PB (i.e. uncoated) and PCB (i.e. paclitaxel-based) was not significantly different (38.7% vs. 35.7%, multiplicity adjusted $P = 0.409$). Our results are consistent with a meta-analysis of 26 randomized clinical trials comparing PCBs vs. non-PCB devices for the treatment of coronary artery disease (i.e. small-vessel disease, bifurcation, acute myocardial infarction, bare-metal stent-ISR, DES-ISR, etc.) showing

no significant difference in mortality between groups and even a possible late survival benefit associated with PCBs.[38]

Finally, in a competing risk analysis confirming the non-significant difference between PCB and PES in the outcome of interest of 10-year target lesion revascularization after accounting for the competing risk of death, we also observed that patients assigned to PES implantation had a higher risk of death than those assigned to PCB angioplasty. The interpretation of this finding is challenging and enhances the need for further analysis of the long-term safety of repeat DES implantation for DES-ISR.

Limitations

The results of this very late outcomes analysis of the ISAR-DESIRE 3 trial should be interpreted considering the following limitations. First, the ISAR-DESIRE 3 trial was originally designed on the surrogate efficacy endpoint of percentage diameter stenosis as assessed by 6–8-month angiography follow-up.[13] The present analysis, designed and approved *post hoc*, relies, therefore, on a limited sample size in relation to clinical outcomes and some non-significant effects and interactions may be influenced by available statistical power. Against this background, the main findings should be confirmed in a larger number of patients. However, the ISAR-DESIRE 3 trial is the largest randomized investigation on DES-ISR conducted thus far and the observation of very high incidences of events, resulting from both follow-up extension and inclusion of patients with on average more complex patterns than *de novo* coronary artery disease investigations, has mitigated sample size limitations. Second, while technology advances from devices used in PB and DCB groups to contemporary iterations are limited, significant improvements have occurred in terms of DESs. In the ISAR-DESIRE 3 trial, first-generation PES was used in the DES group. It is possible, therefore, that the use of a first-generation device has contributed to the results of this analysis and newer types of DES may produce improved outcomes after treatment of DES-ISR. However, a 10-year outcomes analysis with second-generation DES from available randomized clinical trials would still require several years for the achievement of very late follow-up and the present analysis represents the only source of evidence available thus far on the 10-year follow-up of repeat DES implantation for DES-ISR. Third, systematic angiographic follow-up may have influenced the results in terms of target lesion revascularization. However, in the ISAR-DESIRE 3 trial, at 6–8 month angiographic follow-up, percentage diameter stenosis, minimum lumen diameter, and binary restenosis between PCB and PES were quite comparable and results of clinically driven target lesion revascularization were quite consistent with target lesion revascularization.[13] Finally, although the ISAR-DESIRE 3 trial was essentially based on the treatment of first ISR lesions in a previously implanted limus-DES, limited proportions of recurrent ISR were included (19.4%). However, the distribution of multi-layered DES-ISR across treatment groups was balanced in the context of a randomized trial.

Conclusions

Ten years after PCI for DES-ISR, there are no significant differences between PCB angioplasty and PES implantation in the primary device-oriented composite endpoint, major secondary safety endpoint, and major secondary efficacy endpoint of target lesion revascularization. Although differences between devices in 10-year death and cardiac death were not statistically significant, an excess of mortality within 5 years associated with PES and the results of the competing risk analysis indicating a potential risk increase associated with PES are difficult to interpret and warrant further analysis. PB angioplasty for DES-ISR is significantly less effective than PCB angioplasty and PES implantation in preventing recurrent ISR.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

Pre-registered clinical trial number

NCT00987324.

Ethical approval statement

Ethical Approval was not required.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interests statement

T.Ke. is named inventor on a patent application for prevention of restenosis after angioplasty and stent implantation outside the submitted work and received lecture fees from Bayer AG, Pharmaceuticals; J.W. reports speaker fee and institutional grant from Abbott Vascular not related to this work, speaker fee from AstraZeneca not related to this work; M.J. reports speaker fees from Biotronik, personal fees from Orbus Neich, grants and personal fees from Boston Scientific, grants and personal fees from Edwards, personal fees from AstraZeneca, personal fees from Recor, grants from Amgen, not related to the current work, H.S. reports honoraria from AstraZeneca, Bayer Vital, MSD Sharp & Dohme, Novartis, Servier, Sanofi-Aventis, Boehringer Ingelheim, Daiichi Sankyo, Amgen, Pfizer and consulting fees from AstraZeneca, Amgen, MSD Sharp & Dohme, not related to the current work; S.K. reports speaker and consultant fees from AstraZeneca, Bristol Myers Squibb, and Translumina, not related to the current work; the other authors report no conflict of interest.

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