ESC European Society of Cardiology

European Heart Journal (2020) **41**, 3715–3728
doi:10.1093/eurheartj/ehz594

FASTTRACK CLINICAL RESEARCH
Interventional cardiology

Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study)

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Received 6 June 2019; revised 26 June 2019; editorial decision 6 August 2019; accepted 8 August 2019; online publish-ahead-of-print 11 September 2019

See page 3729 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz731)

Aims Consensus is lacking regarding the best treatment for coronary in-stent restenosis (ISR). The two most effective treatments are angioplasty with paclitaxel-coated balloon (PCB) and repeat stenting with drug-eluting stent (DES) but individual trials were not statistically powered for clinical endpoints, results were heterogeneous, and evidence about comparative efficacy and safety in relevant subsets was limited.

Methods and results The Difference in Anti-restenotic Effectiveness of Drug-eluting stent and drug-coated balloon AngiopLasty for the occUrrence of coronary in-Stent restenosis (DAEDALUS) study was a comprehensive, investigator-initiated, collaborative, individual patient data meta-analysis comparing angioplasty with PCB alone vs. repeat stenting with DES alone for the treatment of coronary ISR. The protocol was registered with PROSPERO (CRD42017075007). All 10 available randomized clinical trials were included with 1976 patients enrolled, 1033 assigned to PCB and 943 to DES. At 3-year follow-up, PCB was associated with a significant increase in the risk of target lesion revascularization (TLR) compared with DES [hazard ratio (HR) 1.32, 95% CI 1.02–1.70, $P = 0.035$; number-needed-to-harm

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28.5]. There was a significant interaction between treatment effect and type of restenosed stent ($P = 0.029$) with a more marked difference in patients with DES-ISR and comparable effects in patients with bare-metal stent-ISR. At 3-year follow-up, the primary safety endpoint of all-cause death, myocardial infarction, or target lesion thrombosis was comparable between treatments (HR 0.80, 95% CI 0.58–1.09, $P = 0.152$). A pre-specified subgroup analysis indicated a significant interaction between treatment effect and type of DES used to treat ISR ($P = 0.033$), with a lower incidence of events associated with PCB compared with first-generation DES and similar effect between PCB and second-generation DES (HR 1.06, 95% CI 0.71–1.60, $P = 0.764$). Long-term all-cause mortality was similar between PCB and DES (HR 0.81, 95% CI 0.53–1.22, $P = 0.310$); results were consistent comparing PCB and non-paclitaxel-based DES (HR 1.42, 95% CI 0.80–2.54, $P = 0.235$). Myocardial infarction and target lesion thrombosis were comparable between treatments.

Conclusions In patients with coronary ISR, repeat stenting with DES is moderately more effective than angioplasty with PCB at reducing the need for TLR at 3 years. The incidence of a composite of all-cause death, myocardial infarction, or target lesion thrombosis was similar between groups. The rates of individual endpoints, including all-cause mortality, were not significantly different between groups.

Keywords Percutaneous coronary intervention • Clinical Trials • Drug-coated balloon • Drug-eluting stent • In-stent restenosis • Meta-analysis • Mortality • Paclitaxel

Introduction

In-stent restenosis (ISR) represents the most common cause of treatment failure after percutaneous coronary intervention.[1] ISR not infrequently presents as an acute coronary syndrome and is associated with worse long-term outcomes compared with treatment of de novo coronary artery disease.[2,3]

Although newer generation drug-eluting stent (DES) has significantly reduced the incidence of ISR compared with previous devices, all-comers randomized clinical trials comparing contemporary devices showed cumulative rates of target lesion revascularization (TLR) of ~7–10% at 5-year follow-up.[4,5] Trials with extended follow-up out to 10 years are rare and a recent report showed that approximately one-fifth of patients required TLR at this time points.[6] In addition, bare-metal stents continue to be used occasionally and are associated with high rates of ISR.[7,8]

Several therapies for coronary ISR have been tested in clinical trials.[9] However, paclitaxel-coated balloon (PCB) angioplasty and repeat stenting with DES implantation have emerged as the most effective therapeutic options.[10,11] Indeed, several randomized clinical trials have compared outcomes of patients treated with the two types of device, though none were powered for clinical endpoints and considerable heterogeneity exists in terms of characteristics of included patients, type of restenotic stent, generation of DES used in the repeat stenting arm, and duration of follow-up.[10,11] In addition, concerns have recently emerged regarding a possible higher risk of death in patients treated with paclitaxel-eluting devices for the treatment of peripheral arterial disease.[12]

Against this background, we conducted a comprehensive, collaborative meta-analysis of individual patient data from all available randomized clinical trials comparing the angioplasty with PCB and repeat stenting with DES in patients undergoing treatment for ISR.

Methods

Study design and search strategy

The Difference in Anti-restenotic Effectiveness of Drug-eluting stent and drug-coated balloon AngiopLasty for the occUrrence of coronary in-Stent restenosis (DAEDALUS) study was an investigator-initiated, collaborative individual patient data meta-analysis of randomized clinical trials. Trials could be pooled when all the following eligibility criteria were satisfied: (i) random allocation of treatments; (ii) angioplasty with PCB alone vs. repeat stenting with DES alone; (iii) treatment of coronary ISR; and (iv) clinical follow-up of at least 12 months.

Multiple electronic databases (PubMed, Scopus, ScienceDirect, Web of Science) and archives of major scientific societies and international conferences in the field were searched from 13 November 2006 (date of publication of the first randomized clinical trial on ISR testing PCB) to 15 April 2019. Reports retrieved by literature search were screened for eligibility. Further details on the search strategy and reports selection process are provided in the Supplementary material online. After protocol drafting, the primary investigator of each trial eligible for inclusion was invited to contribute to the DAEDALUS study. Data extraction was coordinated by the primary investigator of each trial. Variables of interest were selected at the study protocol stage according to the clinical relevance and consistency across trials by cross check on original publications. Additional unpublished data, including extension of duration of follow-up and variable standardization, were provided when available in the original databases. All the variables of interest were independently checked for each trial at the German Heart Center of Munich with satisfactory results before generating the dedicated electronic database of the DAEDALUS study. The final database was then created and stored at the coordinating centre.

The study was designed and conducted in keeping with the PRISMA-IPD guidelines (Supplementary material online, *Table S1*)[13] and the protocol was registered with PROSPERO (CRD42017075007). The project was funded in part by the German Ministry of Education and Research (BMBF) through a research grant (#KS2017-236).

The local institutional review boards approved each of the included trials and all patients signed informed, written consent before randomization. Clinical events and angiographic measurements in each trial were adjudicated and assessed by independent clinical events committee and core laboratories, respectively.

Endpoints

The primary efficacy endpoint was TLR defined as any revascularization, either percutaneous or surgical, at the target segment (i.e. in-segment ISR). The primary safety endpoint was a composite of all-cause death, myocardial infarction, or target lesion thrombosis. Death was classified as cardiac or non-cardiac according to the cause; generally, when a clear non-cardiac cause could not be established, the event was considered as cardiac. Myocardial infarction was defined according to clinical symptoms, electrocardiogram, and cardiac biomarkers as defined elsewhere.[14] Academic Research Consortium criteria for definite or probable stent thrombosis were used to define target lesion thrombosis.[14] Ischaemia-driven TLR definition included any revascularization at the target lesion site driven by typical symptoms and objective signs of myocardial ischaemia at non-invasive or invasive testing rather than only binary restenosis at angiography follow-up. Target vessel revascularization was defined as any revascularization, either percutaneous or surgical, of any segment of the target vessel including the target lesion. The composite of all-cause death, myocardial infarction, target lesion thrombosis, or TLR as well as the composite of all-cause death, myocardial infarction, target lesion thrombosis, or target vessel revascularization were included among secondary endpoints to describe the net benefit associated with the two treatments.

Statistical analysis

Statistical analysis was conducted at the German Heart Center of Munich. Nominal variables were reported as counts and percentages and compared by the Pearson χ^2 or Fisher's exact test as appropriate. Continuous variables distribution was assessed by the Shapiro–Wilk test and reported accordingly as mean and standard deviation or median and interquartile range (IQR); continuous variables were compared by the Student's *t* or Mann–Whitney–Wilcoxon *U* test as appropriate.

Outcomes were assessed as time-to-first event according to the intention-to-treat principle. Cumulative incidences were computed according to the Kaplan–Meier method, survival curves plotted along with 95% confidence intervals and numbers at risk, and comparisons performed by the log rank test.[15–17] For each outcome, primary results were obtained by one-stage mixed-effects Cox proportional hazards regression model with treatment assignment as the fixed component and the original trial as the random component.[13,18,19] Resulting risk estimates were reported as HR and 95% confidence interval and *P*-values provided by the Wald test.[15] Proportional hazards assumption was assessed by testing the correlation between Schoenfeld scaled residuals and follow-up time and by inspecting the scaled residuals against transformed time;[15,17] when required Aalen's additive hazards model and time splitting (data-driven landmark analysis) were applied.[15,17] When outcomes resulted significantly different after statistical testing, the number-needed-to-treat or number-needed-to-harm (NNH) was computed as described for survival analysis.[20]

Multivariable adjustment of risk estimates for age, gender, diabetes, hypertension, hypercholesterolaemia, smoking history, prior myocardial infarction, clinical presentation, lesion site, left ventricular ejection fraction, multivessel disease, DES generation, ISR type, ISR length, ISR class, reference vessel diameter, minimum lumen diameter, pre-dilation, and maximum pressure of application after multiple imputation by chained equations for missing data and pooling of datasets by Rubin rules (overall ~3% of missing values) was conducted by mixed-effects model with an additional random effect accounting for multiple lesions per patient.[21]

A two-stage meta-analysis with individual trial risk estimates extraction by Cox proportional hazards regression and subsequent pooling by fixed- and random-effects models was conducted as sensitivity analysis for each outcome.[13,18,19,22] Forest plots reporting pooled and trial-specific effects along with the corresponding relative weight according to the inverse of variance were drawn.[22,23] Heterogeneity between trials was formally explored by the *Q* test and described by between-trial variance τ^2 and I^2 statistic, with values <25%, between 25% and 50%, and >50% describing low, intermediate, and severe heterogeneity, respectively.[22,24]

Planned subgroup analysis by Cox mixed-effects model for the primary safety and efficacy endpoints included the following subsets: age < or ≥65 years old, gender, region of trial conduct, diabetes, smoking history, acute coronary syndrome at admission, ISR angiographic pattern, ISR type, DES generation used in the trial, reference vessel diameter < or ≥2.75 mm, minimum lumen diameter < or ≥median value, and ISR length <20 or ≥20 mm.

Finally, potential sources of bias were assessed by using the Cochrane Collaboration tool,[25] publication bias/small-study effect was explored by funnel plots and Egger test,[22] and overall reliability of the conclusions was presented according to the GRADE system.[26]

Results

Ten prospective, randomized clinical trials[27–36] identified by literature search were eligible for inclusion in the DAEDALUS study. Details about the results of search and screening processes are shown in the Supplementary material online, *Figure S1* and *Table S2*. After formal invitation, the primary investigator of each trial agreed to the collaborative project.

A total of 1976 patients was included (2080 lesions), 1033 (1084 lesions) assigned to PCB and 943 (996 lesions) assigned to DES. Details about the included trials are shown in the *Table 1* and Supplementary material online. The two groups of patients were balanced with respect to baseline clinical characteristics (*Table 2*), though there were some differences in baseline lesion and procedural characteristics (*Table 3*). Patients assigned to PCB received most frequently an iopromide-excipient-based device (84.8%). Patients assigned to repeat stenting with DES received paclitaxel-eluting stent in the three earlier trials (32.0%), everolimus-eluting stent in the six subsequent trials (60.3%), and biolimus-eluting stent (7.6%) in the most recent trial. Follow-up duration was comparable between PCB and DES groups ($P = 0.357$) with a median of 1015 (403–1095) days in the study population.

Primary efficacy endpoint

Clinical outcomes are shown in *Table 4*. With respect to the primary efficacy endpoint, at 3-year follow-up a total of 243 events occurred, 144 in the PCB group (7.14 per 100 person-years) and 99 in the DES group (5.14 per 100 person-years), corresponding to cumulative incidences of 16.0% (IQR 13.5–18.4%) and 12.0% (IQR 9.7–14.3%), respectively ($P = 0.020$) (*Figure 1*). Patients assigned to PCB showed a 32% relative risk increase in TLR compared with those assigned to DES (HR 1.32, 95% CI 1.02–1.70, $P = 0.035$; NNH 28.5). After multivariable adjustment, results remained consistent [adjusted hazard ratio (HR_{adj}) 1.38, 95% CI 1.05–1.82, $P = 0.020$].

Table 1 Main characteristics of the included randomized clinical trials

Trial	Design	Centres Region	Investigation time	Patients (lesions) Total		PCB type	DES type	Restenotic stent
				PCB	DES			
PEPCAD II	1:1 Open-Label Core lab CEC	10 Germany	Jan 2006 – Dec 2006	131 (131) 66 (66)	65 (65)	3 μg/mm^2 Iopromide	Paclitaxel-eluting Durable-polymer Stainless steel (132 μm)	Bare-metal
ISAR DESIRE 3	1:1 Open-Label Core lab CEC	3 Germany	Aug 2009 – Oct 2011	268 (340) 137 (172)	131 (168)	3 μg/mm^2 Iopromide	Paclitaxel-eluting Durable-polymer Stainless steel (132 μm)	Drug-eluting
PEPCAD China ISR	1:1 Open-Label Core lab CEC	17 China	Mar 2011 – Apr 2012	215 (221) 109 (113)	106 (108)	3 μg/mm^2 Iopromide	Paclitaxel-eluting Durable-polymer Stainless steel (132 μm)	Drug-eluting
RIBS V	1:1 Open-Label Core lab CEC	25 Spain	Jan 2010 – Jan 2012	189 (189) 95 (95)	94 (94)	3 μg/mm^2 Iopromide	Everolimus-eluting Durable-polymer Cobalt-Chromium (81 μm)	Bare-metal
SEDUCE	1:1 Open-Label Core lab CEC	2 Belgium	Jun 2009 – Oct 2011	49 (49) 24 (24)	25 (25)	3 μg/mm^2 Iopromide	Everolimus-eluting Durable-polymer Cobalt-chromium (81 μm)	Bare-metal
RIBS IV	1:1 Open-Label Core lab CEC	23 Spain	Jan 2010 – Aug 2013	309 (309) 154 (154)	155 (155)	3 μg/mm^2 Iopromide	Everolimus-eluting Durable-polymer Cobalt-chromium (81 μm)	Drug-eluting
TIS	1:1 Open-Label Core lab CEC	1 Czech Republic	Jan 2012 – Aug 2014	136 (148) 68 (74)	68 (74)	3 μg/mm^2 Iopromide	Everolimus-eluting Durable-polymer Cobalt-chromium (81 μm)	Bare-metal
DARE	1:1 Open-Label Core lab CEC	8 Netherlands	May 2010 – Jun 2015	278 (278) 137 (137)	141 (141)	3 μg/mm^2 Iopromide	Everolimus-eluting Durable-polymer Cobalt-chromium (81 μm)	Bare-metal Drug-eluting
RESTORE	1:1 Open-Label Core lab CEC	10 South Korea	Apr 2013 – Oct 2016	172 (172) 86 (86)	86 (86)	3 μg/mm^2 Iopromide	Everolimus-eluting Durable-polymer Cobalt-chromium (81 μm)	Drug-eluting
BIOLUX-RCT	2:1 Open-Label Core lab CEC	14 Germany, Latvia	Aug 2012 – Jan 2015	229 (243) 157 (163)	72 (80)	3 μg/mm^2 BTHC	Sirolimus-eluting Bioresorbable-polymer Cobalt-chromium (60–80 μm)	Bare-metal Drug-eluting

BTHC, butyryl-tri-hexyl citrate; CEC, clinical events committee.

Two-stage sensitivity meta-analysis with fixed- and random-effects models showed, respectively, borderline and non-statistically significant differences in the risk of TLR between groups (*Figure 1*). The highest relative weights were associated with the ISAR-DESIRE 3, PEPCAD ISR China, and RIBS IV trials. Heterogeneity across the included trials was moderate ($\tau^2 = 0.080$; $I^2 = 44.3\%$).

The analysis of major clinical and angiographic subgroups revealed a significant ($P = 0.029$) interaction between treatments effect and type of restenotic stent (*Figure 2*). Indeed, a similar risk of TLR between PCB and DES was observed in patients who had bare-metal stent-ISR (HR 0.84, 95% CI 0.51–1.38, $P = 0.490$) and an increased risk associated with PCB (HR 1.60, 95% CI 1.19–2.14, $P = 0.002$) was detected in patients who had DES-ISR.

Table 2 Baseline clinical characteristics

	PCB ($n = 1033$)	DES ($n = 943$)	*P*-value
Age (years)	66.7 [59.0–74.0]	66.3 [59.0–73.3]	0.282
Female	242 (23.4)	207 (22.0)	0.434
Diabetes	383 (37.1)	325 (34.5)	0.226
Insulin-requiring	123 (31.9)	121 (37.3)	0.131
Hypertension	780 (75.5)	720 (76.4)	0.661
Hypercholesterolemia	729 (70.6)	657 (69.7)	0.662
Ever-smoked	525 (50.8)	450 (47.7)	0.162
Prior myocardial infarction	518 (50.1)	429 (45.5)	0.041
Clinical presentation			0.965
Silent ischaemia/stable angina	623 (59.7)	559 (59.3)	
Unstable angina	348 (33.7)	327 (34.7)	
NSTEMI	48 (4.6)	43 (4.6)	
STEMI	5 (0.5)	4 (0.4)	
Left ventricular ejection fraction (%)	60 [50–65]	60 [51–65]	0.282
Multivessel disease	475 (46.0)	408 (43.3)	0.378

Data are *n* (%) or median [interquartile range].
NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Table 3 Angiographic and procedural characteristics

	PCB ($n = 1084$)	DES (n = 996)	*P*-value
Target lesion site			0.102
Left main	0	5 (0.5)	
Left anterior descending	451 (41.6)	432 (43.4)	
Left circumflex	238 (22.0)	228 (22.9)	
Right coronary artery	377 (34.8)	316 (31.8)	
Saphenous vein graft	17 (1.6)	13 (1.3)	
Restenotic device			0.810
Bare-metal stent	379 (35.0)	345 (34.6)	
Drug-eluting stent	693 (63.9)	645 (64.8)	
In-stent restenosis morphology			0.048
Focal	606 (55.9)	527 (52.9)	
Diffuse	322 (29.7)	301 (30.2)	
Proliferative	75 (6.9)	81 (8.1)	
Occlusive	28 (2.6)	46 (4.6)	
Focal in-stent restenosis morphology			0.364
Edge or gap	146 (24.1)	131 (24.9)	
Body	369 (60.9)	293 (55.6)	
Multifocal	35 (5.8)	38 (7.2)	
Restenosis length (mm)	9.9 [6.7–15.7]	10.9 [7.6–17.1]	0.0002
Diameter stenosis (%)	68.2 [57.1–77.4]	69.1 [59.6–79.4]	0.004
Minimum lumen diameter (mm)	0.86 [0.60–1.14]	0.79 [0.55–1.10]	0.006
Reference vessel diameter (mm)	2.72 [2.40–3.04]	2.71 [2.41–3.05]	0.874
Pre-dilation	1011 (93.3)	891 (89.5)	0.002
Maximum balloon pressure	14 [12–18]	16 [14–20]	<0.0001

Data are *n* (%) or median [interquartile range].
DES, drug-eluting stent; PCB, paclitaxel-coated balloon.

Table 4 Three-year clinical outcomes

	PCB ($n = 1033$)	DES ($n = 943$)	P_{LR}	HR (95% CI)	P_W	HR_{adj} (95% CI)	P_{adj}
Target lesion revascularization (primary efficacy endpoint)	144 (16.0)	99 (12.0)	0.020	1.32 (1.02–1.70)	0.035	1.38 (1.05–1.82)	0.020
All-cause death, myocardial infarction, or target lesion thrombosis (primary safety endpoint)	75 (9.0)	85 (10.9)	0.182	0.80 (0.58–1.09)	0.152	0.74 (0.52–1.04)	0.085
Death	42 (5.5)	48 (6.6)	0.334	0.81 (0.53–1.22)	0.310	0.68 (0.42–1.10)	0.116
Cardiac death	16 (2.0)	24 (3.3)	0.134	0.61 (0.32–1.15)	0.128	0.61 (0.32–1.19)	0.148
Non-cardiac death	26 (3.6)	24 (3.4)	0.964	1.01 (0.58–1.76)	0.973	0.80 (0.44–1.46)	0.474
Myocardial infarction	41 (4.7)	38 (4.4)	0.941	0.95 (0.61–1.48)	0.820[a]	0.95 (0.59–1.53)	0.829
Target lesion thrombosis	10 (1.2)	8 (0.9)	0.765	1.14 (0.45–2.90)	0.777	1.09 (0.39–3.03)	0.869
Ischaemia-driven target lesion revascularization	129 (14.3)	84 (10.1)	0.011	1.39 (1.06–1.84)	0.018	1.43 (1.07–1.92)	0.016
Target vessel revascularization	161 (17.9)	126 (15.2)	0.173	1.15 (0.91–1.46)	0.235	1.19 (0.92–1.55)	0.184
All-cause death, myocardial infarction, target lesion thrombosis, or target lesion revascularization	197 (22.1)	167 (20.6)	0.384	1.07 (0.87–1.32)	0.518[b]	1.07 (0.84–1.35)	0.593
All-cause death, myocardial infarction, target lesion thrombosis, or target vessel revascularization	207 (23.0)	191 (23.2)	0.945	0.97 (0.80–1.19)	0.796[c]	0.98 (0.78–1.23)	0.851

CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; P_{adj}, *P*-value of the Wald test after multivariable adjustment; P_{LR}, *P*-value of the log rank test; P_W, *P*-value of the Wald test; PCB, paclitaxel-coated balloon.
[a]Aalen additive hazards model with penalization: $P = 0.392$.
[b]Aalen additive hazards model with penalization: $P = 0.944$.
[c]Aalen additive hazards model with penalization: $P = 0.910$.

Primary safety endpoint

With respect to the primary safety endpoint, at 3-year follow-up a total of 160 events occurred, 75 in the PCB group (3.42 per 100 person-years) and 85 in the DES group (4.20 per 100 person-years), corresponding to 3-year cumulative incidences of 9.0% (IQR 7.0–11.0%) vs. 10.9% (IQR 8.6–13.1%), respectively ($P = 0.182$). At primary analysis, the risk of all-cause death, myocardial infarction, or target lesion thrombosis was similar between groups (HR 0.80, 95% CI 0.58–1.09, $P = 0.152$) (*Figure 3*). After multivariable adjustment, the numerical trend favouring PCB remained non-statistically significant (HR_{adj} 0.74, 95% CI 0.52–1.04, $P = 0.085$).

The main results did not change after two-stage meta-analysis, regardless of the model applied (HR 0.79, 95% CI 0.58–1.10, $P = 0.160$) (*Figure 3*). The highest relative weights were associated with the ISAR-DESIRE 3, RIBS IV, BIOLUX-RCT, and RIBS V trials. Heterogeneity was not detected ($\tau^2 = 0$; $I^2 = 0\%$).

Subgroup analysis revealed a significant interaction between treatment effect and generation of DES used for the treatment of ISR ($P = 0.033$) (*Figure 4*): PCB led to lower incidence of adverse events compared with first-generation DES (HR 0.53, 95% CI 0.32–0.87, $P = 0.012$) and similar incidence when compared with second-generation DES (HR 1.06, 95% CI 0.71–1.60, $P = 0.764$).

All-cause death, cardiac death, non-cardiac death, and mortality between paclitaxel-coated balloon and non-paclitaxel-based drug-eluting stent

The incidence of all-cause death was similar between PCB and DES (42 events, 1.87 per 100 person-years and 48 events, 2.30 per 100 person-years; cumulative incidence of 5.5% vs. 6.6%, $P = 0.334$; HR 0.81, 95% CI 0.53–1.22, $P = 0.310$) (*Figure 5*). After multivariable adjustment, results remained consistent (HR_{adj} 0.68, 95% CI 0.42–1.10, $P = 0.116$). The risk of cardiac and non-cardiac death was similar between PCB and DES (HR 0.61, 95% CI 0.32–1.15, $P = 0.128$ and HR 1.01, 95% CI 0.58–1.76, $P = 0.973$, respectively) (*Figure 5*).

Pooling only trials using PCB vs. non-paclitaxel-based DES, the risk of all-cause death was similar between groups (HR 1.42, 95% CI 0.80–2.54, $P = 0.235$), without significant changes after adjustment (HR_{adj} 1.08, 95% CI 0.58–2.08, $P = 0.774$) (*Figure 5*).

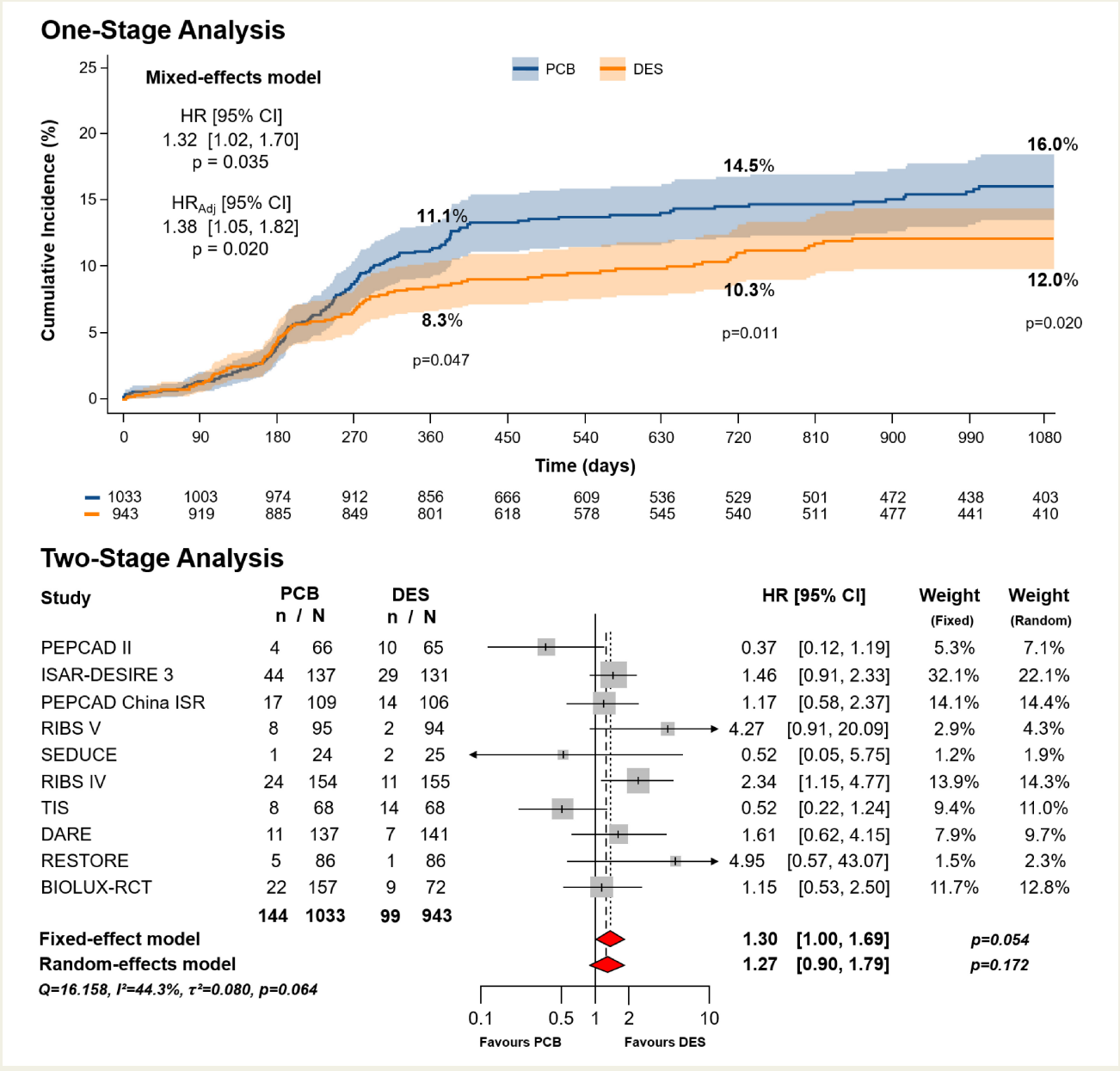


Figure 1 Primary efficacy endpoint (target lesion revascularization). Cumulative incidence of primary efficacy endpoint in patients allocated to angioplasty with paclitaxel-coated balloon vs. repeat stenting with drug-eluting stent. The upper panel shows the results of the one-stage analysis. The lower panel shows the results of the two-stage analysis. CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; HR_{adj}, adjusted hazard ratio; *n*, number of patients with event; *N*, number of patients assigned to the treatment; PCB, paclitaxel-coated balloon. The numbers of patients at risk in the treatment groups are shown below the graphs.

Two-stage sensitivity analyses showed consistent results (Supplementary material online, *Table S3*).

Other secondary endpoints

The risk of myocardial infarction at 3-year follow-up was similar between PCB and DES (HR 0.95, 95% CI 0.61–1.48, $P = 0.820$) (*Table 4*). A different distribution in the occurrence of myocardial infarction over time was observed between the two treatment groups with an early post-procedural trend towards an increased incidence after DES implantation compared with PCB application followed by an opposite trend favouring DES compared with PCB between 7 and 400 days (Supplementary material online, *Table S4*); late occurrence of myocardial infarction was similar between treatments. The risk of target lesion thrombosis at 3-year follow-up was comparable between groups (HR 1.14, 95% CI 0.45–2.90, $P = 0.777$) (*Table 4*). The net composite secondary endpoint deriving from the combination of the primary efficacy and safety endpoints was similar between groups (HR 1.07, 95% CI 0.87–1.32, $P = 0.514$) (Supplementary material online, *Figures S2 and S3*). Similarly, the

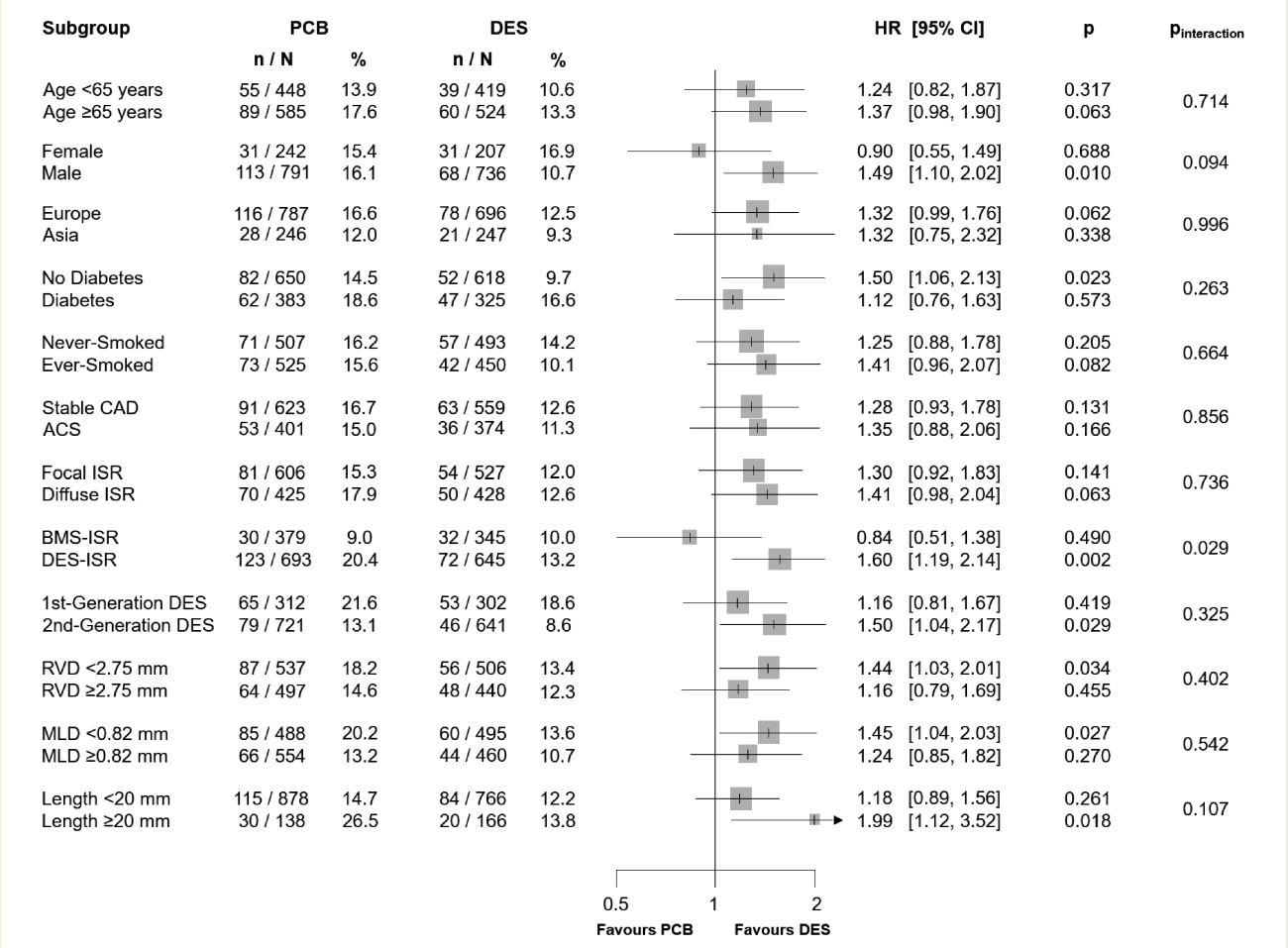


Figure 2 Subgroup analysis for the primary efficacy endpoint. ACS, acute coronary syndrome; BMS, bare-metal stent; CAD, coronary artery disease; CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; ISR, in-stent restenosis; MLD, minimum lumen diameter; *n*, number of patients with event; *N*, number of patients assigned to the treatment; RVD, reference vessel diameter.

other net composite of all-cause death, myocardial infarction, target lesion thrombosis, or target vessel revascularization was comparable between groups (HR 0.97, 95% CI 0.80–1.19, $P = 0.796$) (*Table 4*; Supplementary material online, *Table S4*).

Two-stage sensitivity analyses showed consistent results for all the individual and composite secondary endpoints (Supplementary material online, *Table S3*).

Assessment of bias and reliability of results

Overall, the qualitative assessment of individual trials did not reveal significant sources of bias related to the design and the risk of publication bias/small-study effect was quantified as low (Supplementary material online, *Figures S4 and S5*). The reliability of the conclusions of the study was generally good (Supplementary material online, *Table S5*).

Discussion

In a large-scale, collaborative, individual patient data meta-analysis of patients undergoing treatment for coronary ISR enrolled in the 10 randomized clinical trials comparing angioplasty with PCB and repeat stenting with DES conducted thus far to the best of our knowledge, the main results were as follows (see *Take home figure*):

(1) Angioplasty with PCB is moderately less effective than repeat stenting with DES in terms of the primary efficacy endpoint of TLR;
(2) The incidence of the primary safety endpoint of all-cause death, myocardial infarction, or target lesion thrombosis is similar between treatments, though a numerical increase associated with repeat DES implantation after multivariable adjustment is observed;
(3) The rates of a composite endpoint including both efficacy and safety components are similar between groups.
(4) The rates of all-cause death, cardiac death, and non-cardiac death are similar between treatments and PCB use in the setting of coronary artery disease does not increase long-term mortality compared with non-paclitaxel-based DES.

The findings from the main analysis of the DAEDALUS study should be interpreted in light of a number of considerations. Indeed, the clinical magnitude of the benefit in TLR is moderate and the statistical significance of the risk reduction associated with DES was not confirmed in the two-stage sensitivity analysis as a result of the

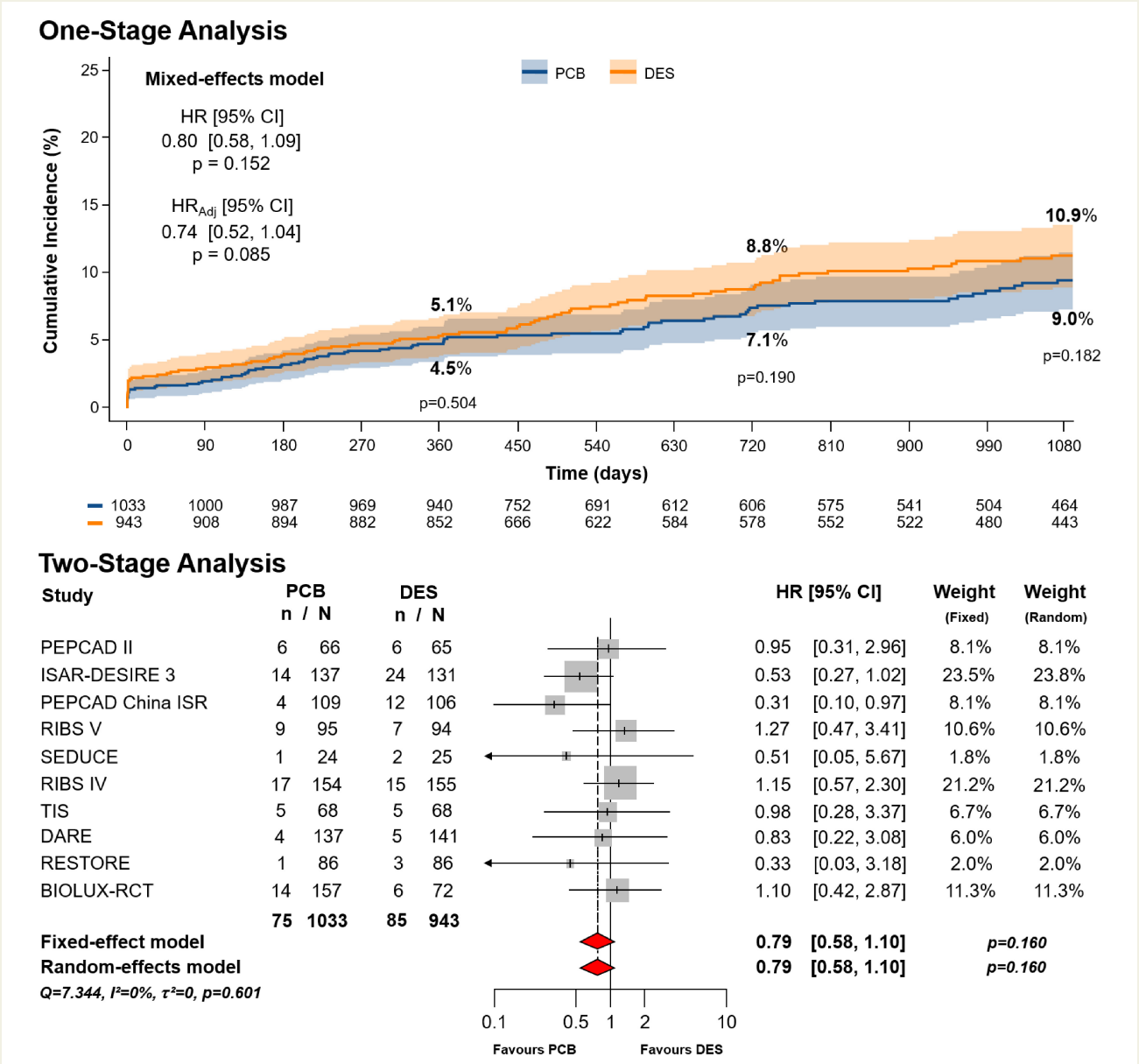


Figure 3 Primary safety endpoint (all-cause death, myocardial infarction, or target lesion thrombosis). Cumulative incidence of primary safety endpoint in patients allocated to angioplasty with paclitaxel-coated balloon vs. repeat stenting with drug-eluting stent. The upper panel shows the results of the one-stage analysis. The lower panel shows the results of the two-stage analysis. CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; HR_{adj}, adjusted hazard ratio; *n*, number of patients with event; *N*, number of patients assigned to the treatment; PCB, paclitaxel-coated balloon. The numbers of patients at risk in the treatment groups are shown below the graphs.

relatively small difference between the two treatments against an intermediate degree of between-trial heterogeneity.[37] In the primary analysis, we estimated that about 29 patients with ISR need to be treated with repeat stenting with DES compared with angioplasty with PCB in order to prevent one TLR.

We observed a significant interaction between treatment effect and type of restenosed stent, with a more pronounced difference in favour of repeat stenting in patients undergoing intervention for DES-ISR and similar effect in patients with bare-metal stent restenosis. This is an interesting finding that found possible correlation with the dissimilar characteristics in types of restenotic tissue after bare-metal and DES implantation.[38] Mixed outcomes after repeat revascularization according to the anatomic pattern have been reported, with DES-ISR generally more challenging to treat and associated with a higher rate of subsequent adverse clinical events compared with bare-metal stent-ISR regardless of the interventional approach.[39]

Although the incidence of the primary safety endpoint of all-cause death, myocardial infarction, or target lesion thrombosis was similar in the two groups, after multivariable adjustment a trend towards a signal of harm after repeat DES implantation was observed.

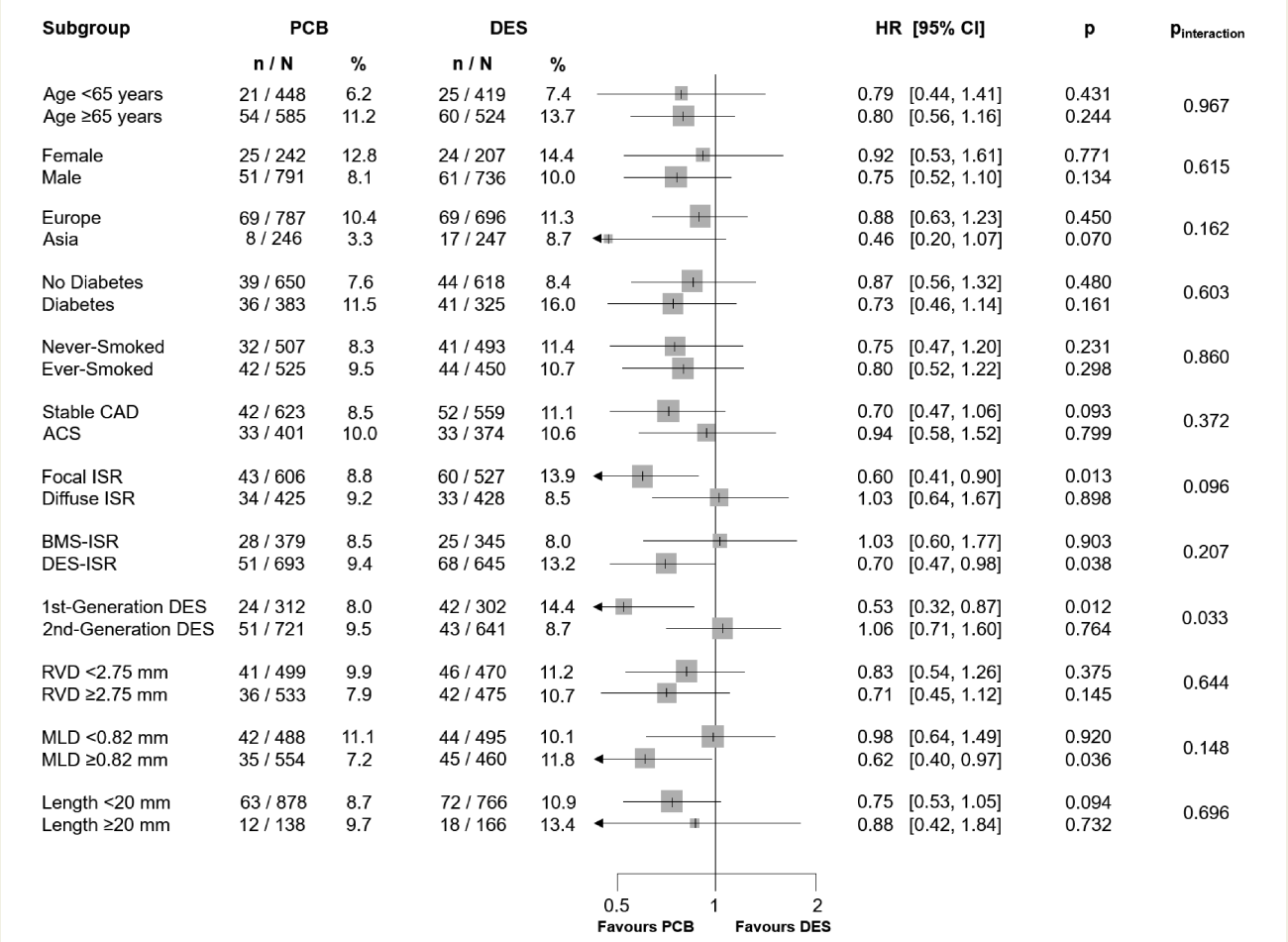


Figure 4 Subgroup analysis for the primary safety endpoint. ACS, acute coronary syndrome; BMS, bare-metal stent; CAD, coronary artery disease; CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; ISR, in-stent restenosis; MLD, minimum lumen diameter; *n*, number of patients with event; *N*, number of patients assigned to the treatment; RVD, reference vessel diameter.

However, there was also evidence of interaction between treatment effect and type of DES used for repeat stenting, with adverse safety signal restricted to patients receiving first-generation DES compared with PCB and quite similar risk of all-cause death, myocardial infarction, and target lesion thrombosis between second-generation DES and PCB at long-term follow-up.

The observations in relation to all-cause death, cardiac death, and non-cardiac death are of some relevance in light of recent analyses suggesting higher all-cause mortality in patients treated with PCB in peripheral arterial disease.[12] In contrast, we did not detect statistically significant differences between angioplasty with PCB and repeat stenting with DES for the treatment of coronary ISR. Importantly, by comparing patients enrolled in trials comparing PCB with non-paclitaxel-based DES (i.e. everolimus- and biolimus-eluting stents), no significant difference in long-term survival was observed.

The risk of myocardial infarction between groups was similar at long-term follow-up. Indeed, the somewhat inferior performance of PCB in terms of acute gain and minimum lumen diameter at surveillance angiography observed in some trials[31,33,35,36] as well as the higher number of TLR during follow-up emerged from our study do not to translate into higher rates of myocardial infarction. Similarly, the incidence of definite or probable target lesion thrombosis was low and comparable between groups proving in a general subset that both possible minor dissections after angioplasty with PCB and double metallic layers after repeat stenting with DES implantation do not seem to significantly influence long-term safety.[1,9]

Current European guidelines on myocardial revascularization recommend the use of either PCB or DES for the treatment of coronary ISR (class of recommendation I, level of evidence A).[40] The results of the DAEDALUS study support the use of both types of device in a mixed population of patients with coronary ISR. The moderate advantage in efficacy of repeat stenting with DES should be weighted against the potential advantages of avoiding additional layers of stent and the absence of significant differences in terms of safety.

Limitations

The present individual patient data meta-analysis shares some of the limitations of the original trials. For example, type of restenotic bare-metal or DES, time from implantation to index intervention for ISR,

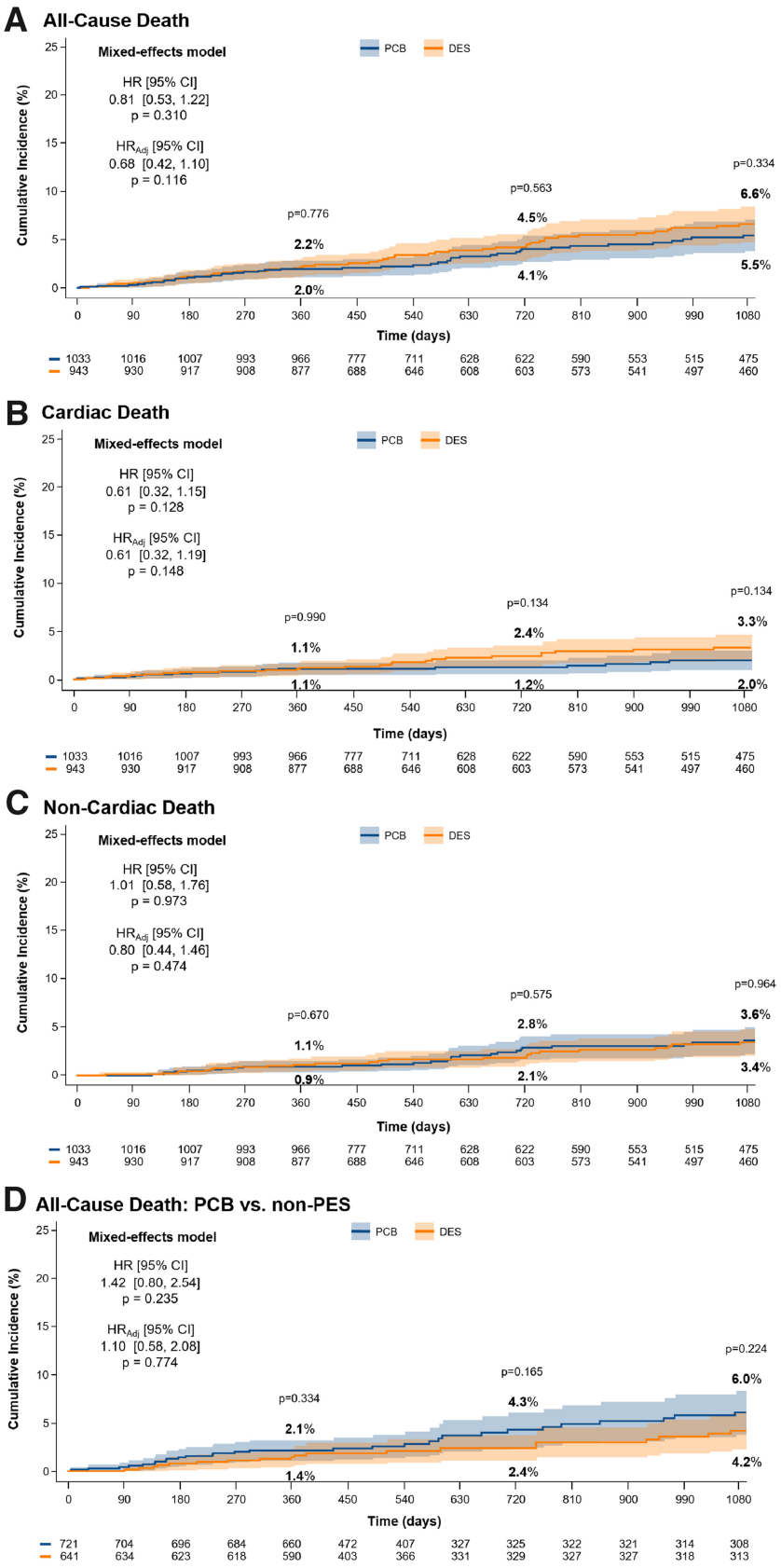
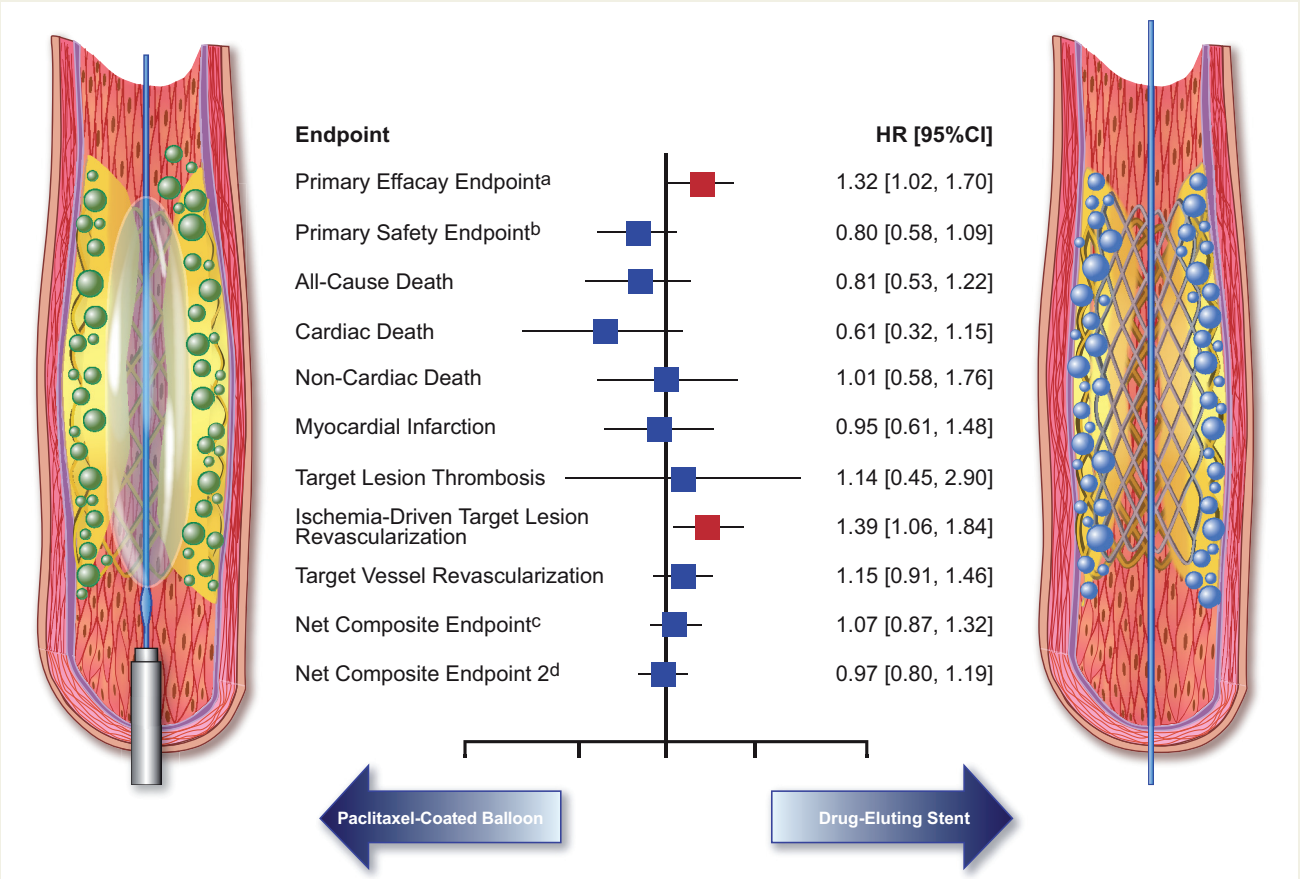


Figure 5 (*A*) All-cause death, (*B*) cardiac death, (*C*) non-cardiac death, for paclitaxel-coated balloon vs. drug-eluting stent, and (*D*) mortality after paclitaxel-coated balloon vs. non-paclitaxel-eluting stent. Incidence and type of death in patients allocated to angioplasty with paclitaxel-coated balloon vs. repeat stenting with drug-eluting stent (*A*–*C*) and paclitaxel-coated balloon vs. non-paclitaxel-eluting stent (*D*). CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; HR_{adj}, adjusted hazard ratio; PCB, paclitaxel-coated balloon. The numbers of patients at risk in the treatment groups are shown below the graphs.



Take home figure Summary of the treatment effects for angioplasty with paclitaxel-coated balloon vs. repeat stenting with drug-eluting stent in patients treated for coronary in-stent restenosis. [a]Primary efficacy endpoint was target lesion revascularization; [b]primary safety endpoint was the composite of death, myocardial infarction, or target lesion thrombosis; [c]net composite endpoint 1 refers to the composite of death, myocardial infarction, target lesion thrombosis, or target lesion revascularization; [d]net composite endpoint 2 refers to the composite of death, myocardial infarction, target lesion thrombosis, or target vessel revascularization.

or endovascular imaging-guided procedures were not uniformly collected across trials. However, the improvement of consistency across trials for several variables, the use of additional unpublished data available in the original databases, and the extension of the follow-up when possible are notable strengths of the study. Specific additional considerations are the following. First, despite inclusion of studies with random treatment allocation, significant differences for some angiographic characteristics were observed at baseline. However, the main findings remained unchanged after multivariable statistical adjustment and some differences are related to the specific technical requirements of angioplasty with PCB (systematic pre-dilation, lower pressure of application, etc.) and DES implantation for ISR (post-dilation, higher pressure of application, etc.). Second, all trials incorporated planned angiographic follow-up as part of the study protocol. This has the advantage of adding information about the mechanisms of recurrent target lesion failure, describing the pattern of reappearance of the disease, and verifying explicitly by standardized measurements the success of the revascularization. However, it has also the potential disadvantage of influencing the natural clinical course of events, producing more revascularizations and related events (e.g. myocardial infarctions) than otherwise would be the case. Nevertheless, restricting analysis to ischaemia-driven TLR did not reveal any significant change from main results. Third, the definition of myocardial infarction was made uniform across trials when possible, but trivial differences could not be overcome in two trials that applied only the definition used in the series of studies of the same research group.[30,32] Fourth, the interesting findings emerging from subgroup analyses need to be interpreted bearing in mind the reduced statistical power after grouping.[41] Finally, although the DAEDALUS study reports the longest available large-scale follow-up of PCB vs. DES for ISR thus far, additional significant benefits or unexpected safety issues related to the two strategies might become apparent only after additional years of observation.

Conclusions

In patients with coronary ISR, angioplasty with PCB is moderately less effective than repeat stenting with DES in reducing TLR at 3-year follow-up. The composite of death, myocardial infarction, or target lesion thrombosis was similar between groups. Individual endpoints, including all-cause death, were not significantly different between groups.

Supplementary material

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

Funding

The work was funded by a research grant from the German Ministry of Education and Research (BMBF; #KS2017-236). The sponsors of the original trials had no role in the study design, data analysis, interpretation and preparation of the manuscript, and submission of the results. The authors had final responsibility for the decision to submit the manuscript for publication.

Conflict of interest: D.G. reports research grant from the European Association of Percutaneous Coronary Intervention. R.A.B. reports lecture fees/honoraria from B Braun Melsungen AG, Biotronik, and Boston Scientific and Micell Technologies, and research funding to the institution from Boston Scientific and Celonova Biosciences. All other authors declared no conflict of interest.

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Corrigendum

doi:10.1093/eurheartj/ehz861
Online publish-ahead-of-print 26 November 2019

Corrigendum to: Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study) [*Eur Heart J* (2020); **41**:3715–3728].

In the originally published version of this article, the following sentence was duplicated in the second paragraph of the Statistical Analysis section: 'The number-needed-to-treat or number-needed-to-harm (NNH) was computed as described for survival analysis'. This has now been removed.