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Drug-Coated Balloon Angioplasty Versus Drug-Eluting Stent Implantation in Patients With Coronary Stent Restenosis

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ABSTRACT

BACKGROUND In patients with coronary in-stent restenosis (ISR) requiring reintervention, it is unclear if the choice of treatment should depend on whether the restenotic stent was a bare-metal stent (BMS) or a drug-eluting stent (DES).

OBJECTIVES This study aimed to assess the comparative efficacy and safety of the 2 most frequently used treatments — angioplasty with drug-coated balloon (DCB) and repeat stenting DES — in patients with BMS-and DES-ISR.

METHODS The DAEDALUS (Difference in Antirestenotic Effectiveness of Drug-Eluting Stent and Drug-Coated Balloon Angioplasty for the Occurrence of Coronary In-Stent Restenosis) study was a pooled analysis of individual patient data from all 10 existing randomized clinical trials comparing DCB angioplasty with repeat DES implantation for the treatment of coronary ISR. In this pre-specified analysis, patients were stratified according to BMS- versus DES-ISR and treatment assigned. The primary efficacy endpoint was target lesion revascularization (TLR) at 3 years. The primary safety endpoint was a composite of all-cause death, myocardial infarction, or target lesion thrombosis at 3 years. Primary analysis was performed by mixed-effects Cox models accounting for the trial of origin. Secondary analyses included nonparsimonious multivariable adjustment accounting also for multiple lesions per patient and 2-stage analyses.

RESULTS A total of 710 patients with BMS-ISR (722 lesions) and 1,248 with DES-ISR (1,377 lesions) were included. In patients with BMS-ISR, no significant difference between treatments was observed in terms of primary efficacy (9.2% vs. 10.2%; hazard ratio [HR]: 0.83; 95% confidence interval [CI]: 0.51 to 1.37) and safety endpoints (8.7% vs. 7.5%; HR: 1.13; 95% CI: 0.65 to 1.96); results of secondary analyses were consistent. In patients with DES-ISR, the risk of the primary efficacy endpoint was higher with DCB angioplasty than with repeat DES implantation (20.3% vs. 13.4%; HR: 1.58; 95% CI: 1.16 to 2.13), whereas the risk of the primary safety endpoint was numerically lower (9.5% vs. 13.3%; HR: 0.69; 95% CI: 0.47 to 1.00); results of secondary analyses were consistent. Regardless of the treatment used, the risk of TLR was lower in BMS- versus DES-ISR (9.7% vs. 17.0%; HR: 0.56; 95% CI: 0.42 to 0.74), whereas safety was not significantly different between ISR types.

CONCLUSIONS At 3-year follow-up, DCB angioplasty and repeat stenting with DES are similarly effective and safe in the treatment of BMS-ISR, whereas DCB angioplasty is significantly less effective than repeat DES implantation in the treatment DES-ISR, and associated with a nonsignificant reduction in the primary composite safety endpoint. Overall, DES-ISR is associated with higher rates of treatment failure and similar safety compared with BMS-ISR.

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Despite the development of drug-eluting stent (DES) generations with increased antirestenotic performance, in-stent restenosis (ISR) remains the primary cause of percutaneous coronary intervention (PCI) failure (1). After stenting with second-generation DES, the incidence of target lesion revascularization (TLR) within 5 years is about 10% and within 10 years is approximately 20% (2,3). Repeat PCI for ISR has been associated with substantial rates of recurrent restenosis and worse survival compared with PCI of de novo coronary artery disease (4–7).

Systematic review evidence shows that drug-coated balloon (DCB) angioplasty and repeat stenting with DES are the most effective treatments for ISR (8). However, thus far, several questions about the comparative clinical efficacy and safety between these 2 treatments have not been adequately addressed for the significant heterogeneity in lesion subtypes and patient subgroups across individual studies (8).

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To date a total of 10 randomized clinical trials comparing DCB with DES have been published (9–18). Recently, we pooled individual patient data from each of these trials in the DAEDALUS (Difference in Antirestenotic Effectiveness of Drug-Eluting Stent and Drug-Coated Balloon Angioplasty for the Occurrence of Coronary In-Stent Restenosis) study (19). The first analysis from this study showed that DES implantation for ISR is moderately more effective than DCB angioplasty in preventing in-segment TLR at long-term follow-up, although no significant differences between treatments were observed for safety endpoints (19).

Currently, it is unclear whether the relative efficacy of DCB angioplasty and repeat stenting with DES depends on the type of restenosed stent. Available evidence is of low quality and largely based on the indirect comparison of results of small, single-arm, observational studies (5,7,20–22). In addition, high-quality, large-scale datasets comparing long-term outcomes after treatment of bare-metal stent (BMS)- versus DES-ISR after PCI are still lacking (7).

Herein, we present the results of a prespecified analysis from the DAEDALUS study that sought to compare long-term outcomes between DCB angioplasty and repeat stenting with DES according to BMS- and DES-ISR and individually assess the relative efficacy and safety of treatments between ISR types.

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent
CI = confidence interval
DCB = drug-coated balloon
DES = drug-eluting stent
HR = hazard ratio
IQR = interquartile range
ISR = in-stent restenosis
PCI = percutaneous coronary intervention
TLR = target lesion revascularization

METHODS

STUDY DESIGN. The DAEDALUS study was an individual patient data pooled analysis of randomized clinical trials that sought to address the uncertainty surrounding the contemporary treatment of coronary ISR (19). The protocol of the study was registered (CRD42017075007) with PROSPERO (International Prospective Register of Systematic Reviews). The study was conducted in keeping with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) individual patient data statement and was supported by the German Ministry of Education and Research (19,23).

A total of 10 trials including 1,976 patients undergoing PCI for coronary ISR by random assignment to DCB or DES have been conducted thus far (9–19). Information on search and selection processes is reported in the Supplemental Appendix. Briefly, included randomized clinical trials compared DCB angioplasty alone versus DES implantation alone for the treatment of ISR at a clinical follow-up time of at least 12 months (9–19). Each trial was approved by its local institutional review board, and all patients signed informed, written consent before

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randomization (9–19). Clinical events and angiographic measurements in each trial were adjudicated and assessed by independent clinical events committee and core laboratory, respectively (9–19).

The primary investigators of each trial agreed to participate in the DAEDALUS study. Data extraction was conducted by the primary investigator of each trial and validated, entered into a dedicated study database, and centrally analyzed at the coordinating center, the German Heart Center in Munich. Variables of interest were selected at the study protocol stage according to clinical relevance and consistency across trials. Additional data were acquired, including follow-up extension and standardization of variables, when feasible.

Information on the qualitative assessment of each trial is reported in the Supplemental Appendix.

ENDPOINTS. The primary efficacy endpoint was TLR defined as any revascularization, percutaneous or surgical, due to recurrent stenosis of the target lesion segment (24). The primary safety endpoint was a composite of all-cause death, myocardial infarction, or target lesion thrombosis.

Death was classified as all-cause, cardiac, and noncardiac (24). Myocardial infarction, ischemia-driven TLR, and target lesion thrombosis were defined based on the definitions of the Academic Research Consortium (24). Target vessel revascularization was defined as any revascularization, percutaneous or surgical, of the target vessel (24).

Secondary net endpoints included the composite of all-cause death, myocardial infarction, target lesion thrombosis, or TLR, and the composite of all-cause death, myocardial infarction, target lesion thrombosis, or target vessel revascularization.

STATISTICAL ANALYSIS. Nominal variables were reported as counts and percentages and compared by the Pearson chi-square or Fisher exact test, as appropriate. Continuous variables distribution was assessed by the Shapiro-Wilk test and reported accordingly as mean ± SD or median (interquartile range [IQR]). Continuous variables were compared by the Student's *t*-test or Mann-Whitney-Wilcoxon *U* test, as appropriate.

Analyses were conducted according to the intention-to-treat principle. Primary analysis was accomplished by 1-stage mixed-effects Cox proportional hazards regression models with treatment assignment as the fixed component and the original trial as the random component. Risks estimates were reported as hazard ratio (HR) and 95% confidence interval (CI) along with p values provided by the Wald-type test (25). 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 (25). A piece-wise additive mixed-effects model accounting for time-varying effects was used when hazards were nonproportional (26). After multiple imputation by chained equations, multivariable adjustment of risk estimates was conducted by lesion-level mixed-effects model or lesion-level piece-wise additive mixed-effects model, as appropriate (26,27); both models were accounting for multiple lesions per patient. The variables included in the models were age, sex, diabetes, hypertension, hypercholesterolemia, smoking history, prior myocardial infarction, clinical presentation, lesion site, left ventricular ejection fraction, multivessel disease, DES generation, ISR length, ISR class, reference vessel diameter, minimum lumen diameter, pre-dilation, and maximum pressure of application. Results of models from each imputed dataset were combined according to the Rubin's rules (26,27). The incidences of events at 3 years were computed according to the Kaplan-Meier method and outcomes between groups over time were compared by the log-rank test (25).

In the BMS- versus DES-ISR analyses, a similar methodology was used. Crude estimates were drawn by Cox proportional hazards regression or piece-wise additive model, as appropriate. Multivariable adjustment was based on mixed-effects Cox model or piecewise additive mixed-effects model accounting for multiple lesions per patient after multiple imputations. In these models, ISR type was the grouping variable. In multivariable models, treatment assigned was among the covariates included.

A 2-stage 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 (28). Heterogeneity between trials was formally explored by the *Q* test and described by between-trial variance τ^2 and I^2 statistics, with values <25%, between 25% and 50%, and >50% describing low, intermediate, and severe heterogeneity, respectively (29).

RESULTS

A total of 710 patients with BMS-ISR (724 lesions) and 1,248 with DES-ISR (1,338 lesions) underwent treatment by DCB angioplasty or repeat stenting with DES across 10 randomized clinical trials (Supplemental Appendix, Supplemental Figure 1, Supplemental Table 1). From the overall pooled dataset, 18

TABLE 1 Clinical Characteristics According to DCB and DES in the Subsets of BMS- and DES-ISR

	BMS-ISR			DES-ISR		
	DCB (n = 372)	DES (n = 338)	p Value	DCB (n = 649)	DES (n = 599)	p Value
Age, yrs	66.5 (59.0–74.8)	66.2 (58.7–73.0)	0.182	66.7 (59.0–73.5)	66.4 (59.0–73.5)	0.927
Female	96 (25.8)	65 (19.2)	0.037	142 (21.9)	141 (23.5)	0.484
Diabetes	109 (29.3)	78 (23.1)	0.060	271 (41.8)	244 (40.7)	0.714
Insulin-requiring	37 (33.6)	30 (38.0)	0.539	86 (31.6)	89 (36.8)	0.218
Hypertension	285 (75.6)	264 (78.1)	0.635	489 (75.3)	452 (75.5)	0.963
Hypercholesterolemia	291 (78.2)	252 (74.6)	0.250	432 (66.6)	401 (66.9)	0.887
Ever-smoked	196 (52.8)	178 (52.7)	0.964	327 (50.4)	270 (45.1)	0.061
Prior myocardial infarction	222 (59.7)	179 (53.1)	0.078	290 (44.7)	248 (41.4)	0.242
Clinical presentation			0.962			0.770
Silent ischemia and/or stable angina	241 (65.3)	214 (64.8)		377 (58.4)	343 (57.5)	
Unstable angina	82 (22.2)	78 (23.6)		260 (40.4)	245 (41.0)	
NSTEMI	41 (11.1)	34 (10.3)		7 (1.1)	9 (1.5)	
STEMI	5 (1.4)	4 (1.2)		0	0	
LVEF, %	59 (50–62)	60 (50–62)	0.758	60 (52–65)	60 (54–65)	0.224
Multivessel disease	161 (51.6)	155 (55.8)	0.371	314 (53.9)	253 (48.3)	0.064

Values are median (interquartile range) or n (%).

BMS = bare-metal stent; DCB = drug-coated balloon; DES = drug-eluting stent; ISR = in-stent restenosis; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

patients were excluded due to missing information on the type of restenosed stent.

Baseline characteristics are reported in Table 1 and overall were well balanced between patients treated with DCB and DES, both in the BMS- and DES-ISR groups. Angiographic and procedural characteristics are reported in Table 2. Significant differences between treatments were detected

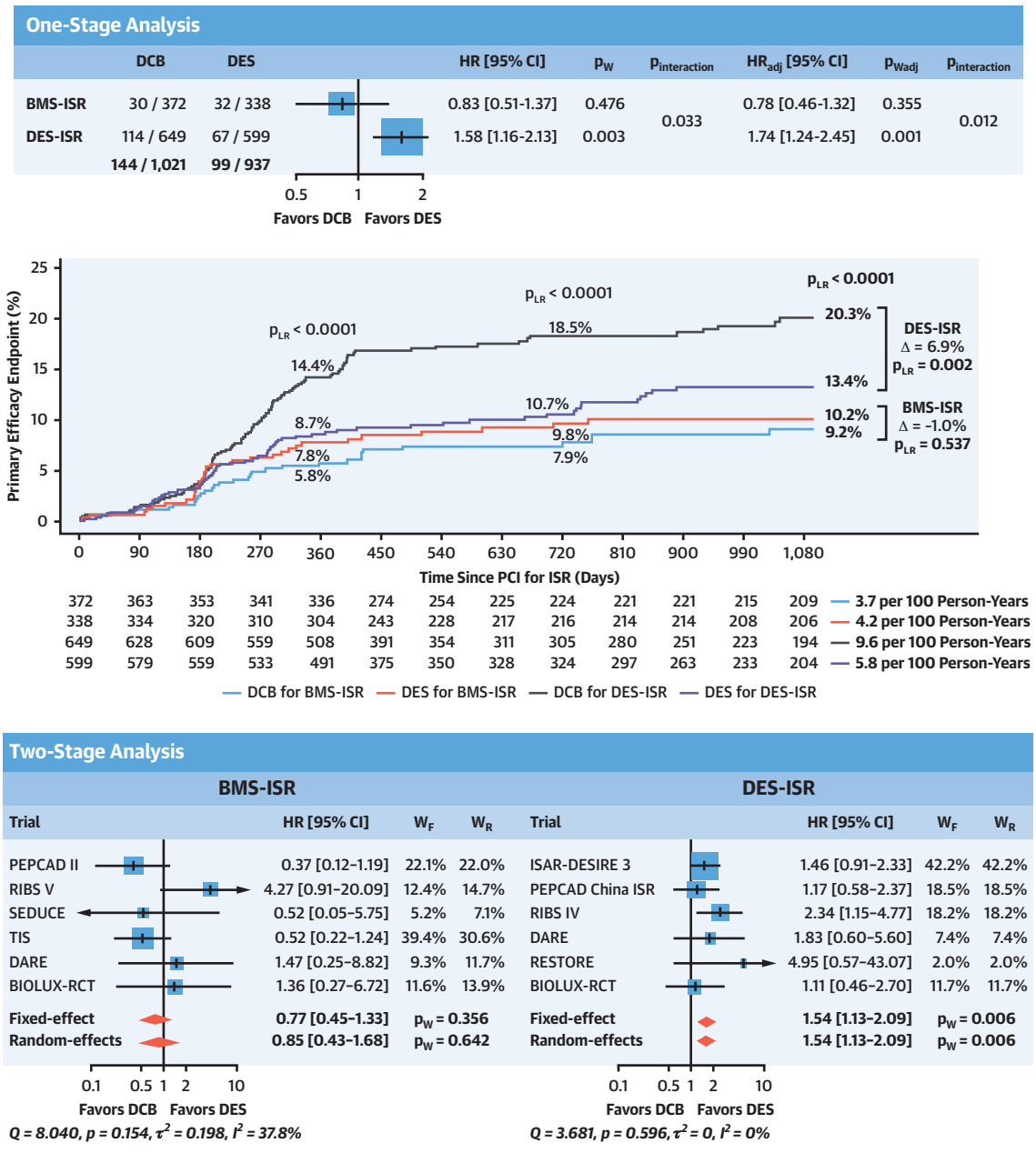
TABLE 2 Angiographic and Procedural Characteristics According to DCB and DES in the Subsets of BMS- and DES-ISR

	BMS-ISR			DES-ISR		
	DCB (n = 379)	DES (n = 345)	p Value	DCB (n = 693)	DES (n = 645)	p Value
Target lesion site			0.283			0.157
Left main	0	1 (0.3)		0	4 (0.6)	
Left anterior descending	148 (39.2)	152 (44.2)		298 (43.0)	278 (43.2)	
Left circumflex	89 (23.5)	77 (22.4)		147 (21.2)	149 (23.1)	
Right coronary artery	137 (36.2)	107 (31.1)		236 (34.1)	207 (32.1)	
Saphenous vein graft	4 (1.1)	7 (2.0)		12 (1.7)	6 (0.9)	
ISR morphology			0.007			0.645
Focal	165 (45.0)	125 (37.1)		438 (66.7)	399 (64.9)	
Diffuse	151 (41.1)	144 (42.7)		169 (25.7)	157 (25.5)	
Proliferative	45 (12.3)	48 (14.2)		29 (4.4)	33 (5.4)	
Occlusive	6 (1.6)	20 (5.9)		21 (3.2)	26 (4.2)	
Focal ISR morphology			0.010			0.579
Edge or gap	29 (21.0)	38 (36.9)		117 (28.5)	93 (25.9)	
Body	101 (73.2)	56 (54.4)		267 (65.0)	237 (66.0)	
Multifocal	8 (5.8)	9 (8.7)		27 (6.6)	29 (8.1)	
Restenosis length, mm	11.9 (7.8–8.6)	12.6 (8.6–19.3)	0.064	9.0 (6.2–13.7)	9.9 (7.1–15.5)	0.001
Diameter stenosis, %	67.2 (56.6–75.2)	69.1 (60.3–78.4)	0.006	68.6 (57.7–78.4)	69.2 (59.6–79.5)	0.120
Minimum lumen diameter, mm	0.89 (0.66–1.16)	0.79 (0.58–1.09)	0.002	0.83 (0.56–1.13)	0.79 (0.54–1.10)	0.188
Reference vessel diameter, mm	2.76 (2.40–3.11)	2.71 (2.41–3.00)	0.213	2.71 (2.40–3.01)	2.71 (2.40–3.08)	0.318
Pre-dilation	368 (97.4)	298 (86.6)	<0.001	627 (92.1)	582 (92.2)	0.912
Maximum balloon pressure, atm	15 (12–18)	16 (14–20)	<0.001	14 (12–18)	18 (14–20)	<0.001

Values are n (%) or median (interquartile range).

Abbreviations as in Table 1.

FIGURE 1 DCB Angioplasty Versus Repeat Stenting With DES According to ISR Type: Primary Efficacy Endpoint



(Top) Main analysis by 1-stage mixed-effects Cox model before and after multivariable adjustment is illustrated by forest plots. **(Middle)** Distribution of the events over time across groups is illustrated by Kaplan-Meier analysis. Pair-wise log-rank test p values by Bonferroni correction for multiple comparisons are reported in the Supplemental Appendix. **(Bottom)** Two-stage sensitivity analyses are illustrated by forest plots. BIOLUX-RCT = Biotronik—Clinical Performance of the Pantera LUX Paclitaxel Coated Balloon Versus the Drug Eluting Orsiro Hybrid Stent System in Patients With In-Stent Restenosis—A Randomized Controlled Trial; BMS = bare-metal stent; CI = confidence interval; DARE = Drug-Eluting Balloon for In-Stent Restenosis; DCB = drug-coated balloon; DES = drug-eluting stent; HR = hazard ratio; HR_{adj} = hazard ratio after multivariable adjustment; ISAR-DESIRE 3 = Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches; ISR = in-stent restenosis; PCI = percutaneous coronary intervention; PEPCAD China ISR = A Safety and Efficacy Study of Paclitaxel-Eluting Balloon to Paclitaxel-Eluting Stent; PEPCAD II = The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to Treat In-Stent Restenoses; $p_{interaction}$ = p value for treatment-by-subgroup interaction; p_{LR} = p value of the log-rank test; p_W = p value of the Wald-type test; p_{Wadj} = p value of the Wald-type test after multivariable adjustment; RESTORE = The Treatment of Drug-Eluting Stent Restenosis Using Drug-Eluting Stents Versus Drug Coated Balloon for Preventing Recurrent In-Stent Restenosis; RIBS IV = Restenosis Intra-Stent of Drug-Eluting Stents: Paclitaxel-Eluting Balloon vs. Everolimus-Eluting Stent; RIBS V = Restenosis Intra-Stent of Bare-Metal Stents: Paclitaxel-Eluting Balloon vs Everolimus-Eluting Stent; SEDUCE = Safety and Efficacy of a Drug Eluting Balloon in Coronary Artery Restenosis; TIS = Treatment of In-Stent Restenosis; W_F = relative weights by fixed-effect model; W_R = relative weights by random-effects model.

TABLE 3 Clinical Outcomes at 3-Year Follow-Up Between DCB and DES According to BMS- and DES-ISR

	BMS-ISR					DES-ISR					
	DCB	DES	p_{LR}	HR (95% CI)	p_W	DCB	DES	p_{LR}	HR (95% CI)	p_W	$p_{interaction}$
Target lesion revascularization	30 (9.2)	32 (10.2)	0.537	0.83 (0.51–1.37)	0.467	114 (20.3)	67 (13.4)	0.002	1.58 (1.16–2.13)	0.003	0.033
All-cause death, myocardial infarction, or target lesion thrombosis	28 (8.7)	23 (7.5)	0.672	1.13 (0.65–1.96)	0.673	47 (9.5)	62 (13.3)	0.058	0.69 (0.47–1.00)	0.051	0.146
All-cause death	18 (5.8)	12 (4.0)	0.353	1.41 (0.68–2.92)	0.360	24 (5.5)	36 (8.5)	0.064	0.61 (0.37–1.03)	0.065	0.070
Cardiac death	7 (2.0)	6 (2.0)	0.885	1.08 (0.36–3.23)	0.885	9 (2.0)	18 (4.3)	0.053	0.46 (0.21–1.03)	0.060	0.218
Noncardiac death	11 (3.8)	6 (2.0)	0.268	1.75 (0.65–4.73)	0.272	15 (3.5)	18 (4.4)	0.454	0.77 (0.39–1.52)	0.450	0.182
Myocardial infarction	13 (4.0)	13 (4.1)	0.830	0.92 (0.43–1.98)	0.823	28 (5.2)	25 (4.6)	0.937	0.99 (0.58–1.70)	0.971	0.876
Target lesion thrombosis	4 (1.2)	2 (0.6)	0.465	1.83 (0.34–10.02)	0.485	6 (1.2)	6 (1.1)	0.888	0.92 (0.30–2.86)	0.889	0.510
Ischemia-driven target lesion revascularization	26 (7.9)	27 (8.7)	0.663	0.87 (0.51–1.49)	0.619	103 (18.4)	57 (11.2)	0.001	1.67 (1.21–2.31)	0.002	0.044
Target vessel revascularization	36 (10.9)	43 (13.7)	0.211	0.74 (0.48–1.15)	0.185	125 (22.3)	83 (16.2)	0.014	1.39 (1.05–1.84)	0.021	0.019
All-cause death, myocardial infarction, target lesion thrombosis, or target lesion revascularization	52 (15.6)	50 (15.8)	0.772	0.93 (0.63–1.37)	0.700	145 (26.5)	117 (23.9)	0.185	1.15 (0.90–1.47)	0.251	0.349
All-cause death, myocardial infarction, target lesion thrombosis, or target vessel revascularization	57 (17.0)	60 (18.9)	0.385	0.83 (0.58–1.20)	0.326	150 (27.2)	131 (26.2)	0.552	1.06 (0.84–1.34)	0.640	0.281

Values in the columns entitled DCB and DES are n (%), with incidences calculated by Kaplan-Meier method.

CI = confidence interval; HR = hazard ratio; $p_{interaction}$ = p value for treatment-by-subgroup interaction; p_{LR} = p value of the log-rank test; p_W = p value of the Wald-type test; other abbreviations as in Table 1.

with respect to ISR morphology variants, ISR length, minimum lumen diameter, diameter stenosis, lesion pre-dilation, and maximum balloon pressure.

Follow-up length was not significantly different between DCB and DES both in BMS-ISR (median: 1,095 [IQR: 536 to 1,095] days vs. 1,095 [IQR: 539 to 1,095] days; p = 0.147) and DES-ISR (median: 868 [IQR: 413 to 1,080] days vs. 904 [IQR: 369 to 1,095) days; p = 0.916) settings.

Qualitative assessment of individual trials did not show overall relevant sources of bias in study design, with the exception of the unfeasible masking of operators due to constitutive differences between devices (Supplemental Figure 2).

PRIMARY EFFICACY ENDPOINT. Although no significant difference between treatments was observed in BMS-ISR (9.2% vs. 10.2%; HR: 0.83; 95% CI: 0.51 to 1.37), in DES-ISR the risk of TLR was significantly higher after DCB angioplasty than after repeat DES implantation (20.3% vs. 13.4%; HR: 1.58; 95% CI: 1.16 to 2.13), and there was a significant treatment-by-subgroup interaction ($p_{interaction}$ = 0.033) (Figure 1, top; Table 3).

After multivariable adjustment results did not change (BMS-ISR: HR_{adj}: 0.78; 95% CI: 0.46 to 1.32; DES-ISR: HR_{adj}: 1.74; 95% CI: 1.24 to 2.45; $p_{interaction}$ = 0.012) (Figure 1, top; Table 4).

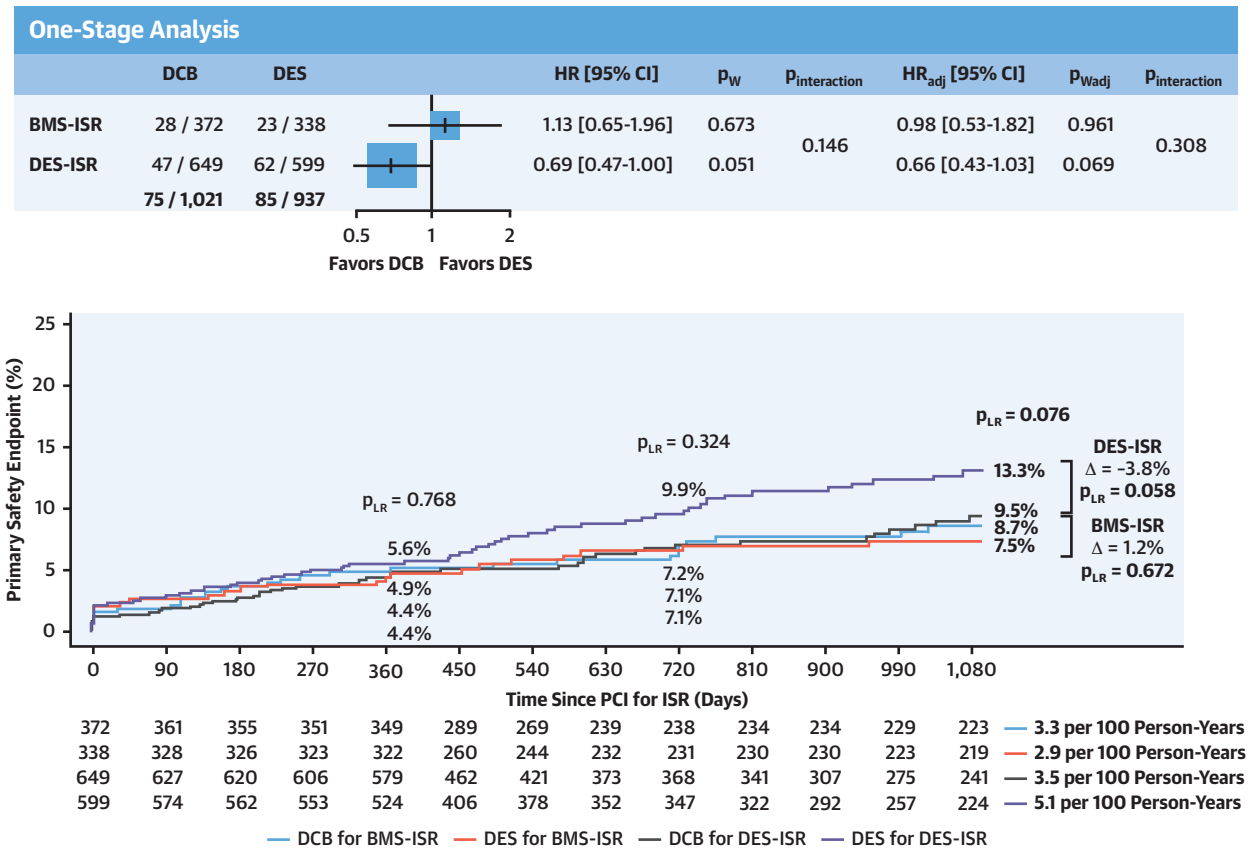
The cumulative incidence of TLR at 3-year follow-up was significantly different across the 4 groups,

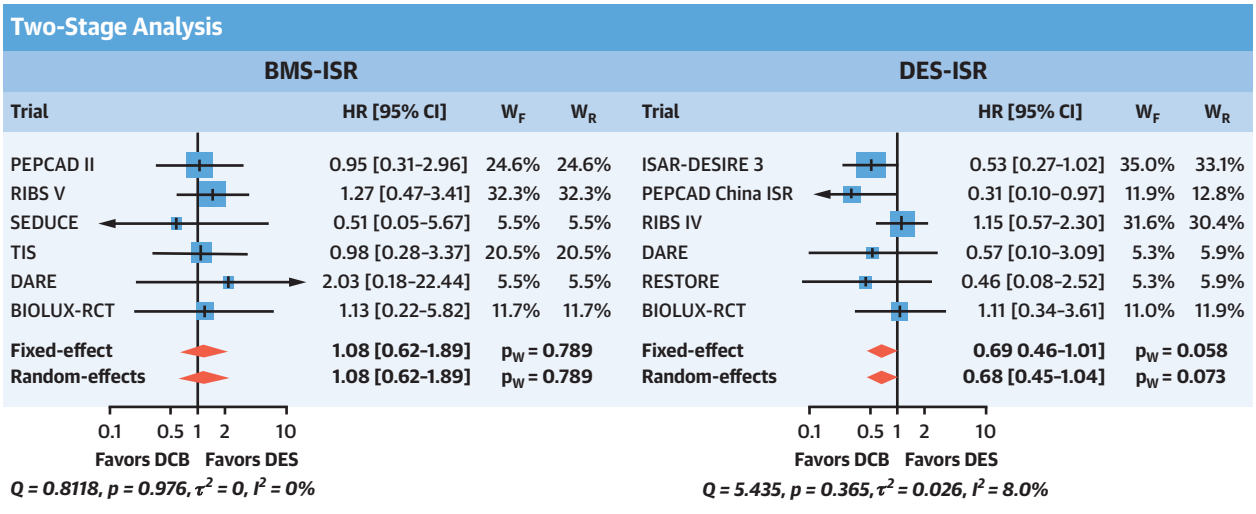
TABLE 4 Clinical Outcomes at 3-Year Follow-Up Between DCB and DES According to BMS- and DES-ISR After Multivariable Adjustment

	BMS-ISR		DES-ISR		
	HR_{adj} (95% CI)	p_{Wadj}	HR_{adj} (95% CI)	p_{Wadj}	$p_{interaction}$
Target lesion revascularization	0.78 (0.46–1.32)	0.355	1.74 (1.24–2.45)	0.001	0.012
All-cause death, myocardial infarction, or target lesion thrombosis	0.98 (0.53–1.82)	0.961	0.66 (0.43–1.03)	0.069	0.308
All-cause death	1.25 (0.55–2.80)	0.594	0.52 (0.26–1.06)	0.073	0.114
Cardiac death	1.06 (0.28–4.00)	0.931	0.51 (0.23–1.14)	0.102	0.355
Noncardiac death	1.22 (0.42–3.56)	0.711	0.58 (0.27–1.27)	0.175	0.273
Myocardial infarction	0.88 (0.37–2.09)	0.767	1.02 (0.56–1.86)	0.939	0.774
Target lesion thrombosis	1.03 (0.14–7.44)	0.980	1.02 (0.30–3.50)	0.975	0.996
Ischemia-driven target lesion revascularization	0.87 (0.49–1.54)	0.623	1.71 (1.21–2.43)	0.003	0.047
Target vessel revascularization	0.70 (0.44–1.13)	0.142	1.49 (1.06–2.08)	0.020	0.011
All-cause death, myocardial infarction, target lesion thrombosis, or target lesion revascularization	0.85 (0.55–1.29)	0.440	1.21 (0.90–1.62)	0.205	0.176
All-cause death, myocardial infarction, target lesion thrombosis, or target vessel revascularization	0.75 (0.50–1.13)	0.172	1.13 (0.84–1.51)	0.425	0.115

HR_{adj} = hazard ratio after multivariable adjustment; other abbreviations as in Tables 1 and 3.

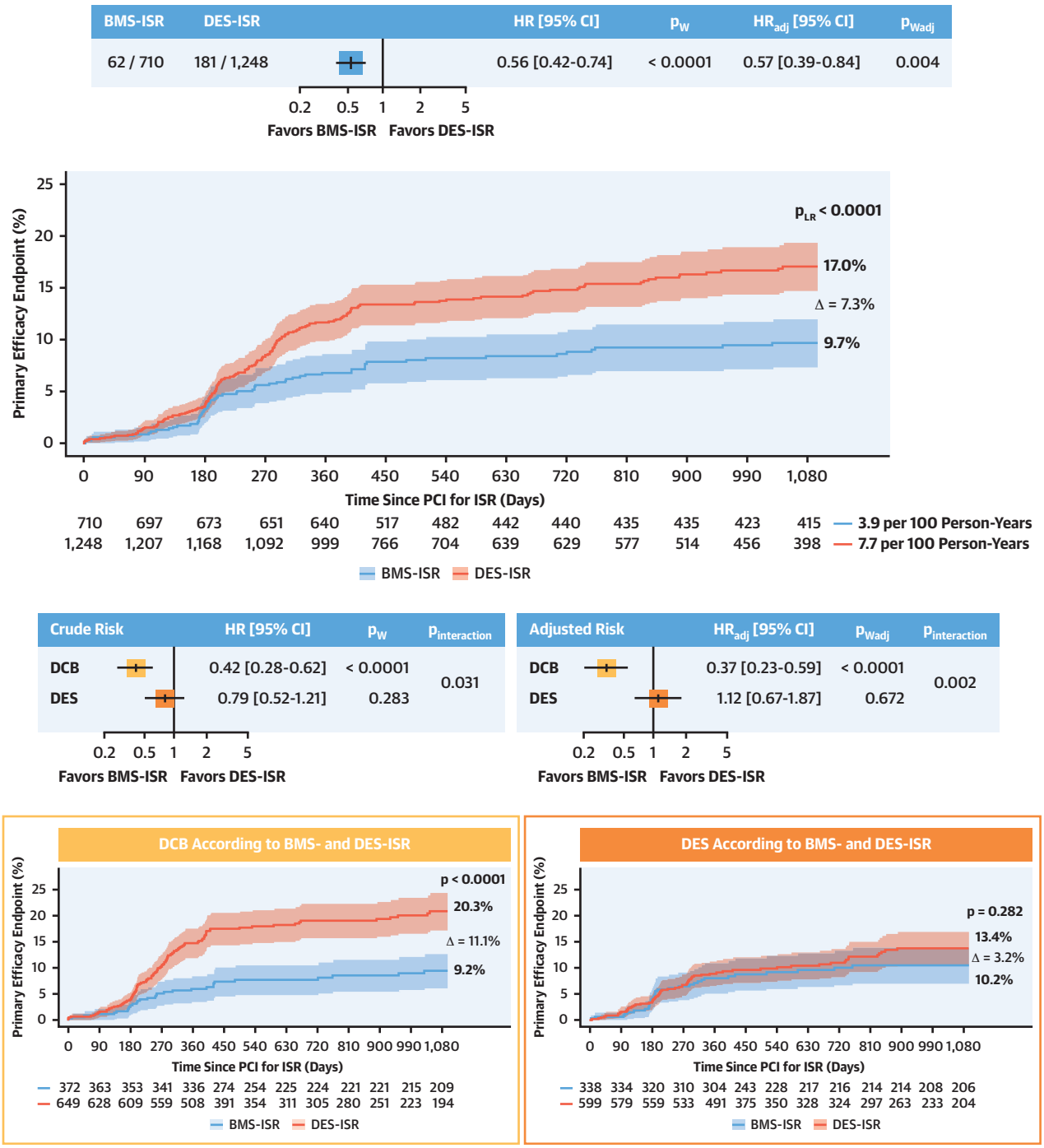
FIGURE 2 DCB Angioplasty Versus Repeat Stenting With DES According to ISR Type: Primary Safety Endpoint





(Top) Main analysis by 1-stage mixed-effects Cox model before and after multivariable adjustment is illustrated by forest plots. **(Middle)** Distribution of the events over time across groups is illustrated by Kaplan-Meier analysis. Pair-wise log-rank test p values by Bonferroni correction for multiple comparisons are reported in the Supplemental Appendix. **(Bottom)** Two-stage sensitivity analyses are illustrated by forest plots. Abbreviations as in Figure 1.

FIGURE 3 BMS- Versus DES-ISR: Primary Efficacy Endpoint



(Top) Crude and multivariable-adjusted risk estimates between BMS- and DES-ISR are illustrated. **(Middle)** Distribution of the events over time by ISR type is illustrated by Kaplan-Meier analysis. Crude **(left)** and multivariable-adjusted **(right)** risk estimates for DCB **(yellow squares)** and DES **(orange squares)** according to BMS- versus DES-ISR are reported by forest plots. **(Bottom)** Distribution of the events over time for DCB **(left)** and DES **(right)** according to BMS- versus DES-ISR are illustrated by Kaplan-Meier analysis. Abbreviations as in Figure 1.

TABLE 5 Clinical Outcomes at 3-Year Follow-Up by ISR Type

	BMS-ISR	DES-ISR	p_{LR}	HR (95% CI)	p_W	HR_{adj} (95% CI)	p_{Wadj}
Target lesion revascularization	62 (9.7)	181 (17.0)	<0.0001	0.56 (0.42–0.74)	<0.0001	0.57 (0.39–0.84)	0.004
All-cause death, myocardial infarction, or target lesion thrombosis	51 (8.1)	109 (11.3)	0.099	0.75 (0.54–1.07)*	0.116*	0.85 (0.58–1.25)*	0.404*
All-cause death	30 (4.9)	60 (6.9)	0.282	0.86 (0.55–1.35)*	0.520*	1.21 (0.74–1.99)*	0.454*
Cardiac death	13 (2.0)	27 (3.1)	0.435	0.81 (0.40–1.66)*	0.568*	0.98 (0.43–2.23)*	0.959*
Noncardiac death	17 (2.9)	33 (3.9)	0.457	0.80 (0.45–1.44)	0.458	1.25 (0.59–2.63)	0.563
Myocardial infarction	26 (4.1)	53 (4.9)	0.419	0.82 (0.52–1.32)	0.419	0.73 (0.37–1.44)	0.364
Target lesion thrombosis	6 (0.9)	12 (1.1)	0.729	0.84 (0.32–2.24)	0.729	0.94 (0.30–2.97)	0.913
Ischemia-driven target lesion revascularization	53 (8.3)	160 (15.0)	<0.0001	0.54 (0.40–0.74)	<0.0001	0.56 (0.35–0.88)	0.013
Target vessel revascularization	79 (12.3)	208 (19.4)	0.0002	0.62 (0.48–0.80)	0.0003	0.70 (0.45–1.10)	0.125
All-cause death, myocardial infarction, target lesion thrombosis, or target lesion revascularization	102 (15.7)	262 (25.3)	<0.0001	0.61 (0.48–0.77)*	<0.0001*	0.67 (0.52–0.86)	0.001*
All-cause death, myocardial infarction, target lesion thrombosis, or target vessel revascularization	117 (17.9)	281 (26.7)	0.0002	0.64 (0.52–0.80)*	<0.0001*	0.68 (0.54–0.86)	0.001*

Values in the columns entitled DCB and DES are n (%), with incidences calculated by Kaplan-Meier method. *Piece-wise additive model.
Abbreviations as in Tables 1, 3, and 4.

defined by the type of restenosed stent and allocated treatment ($p < 0.0001$) (Figure 1, middle).

Two-stage sensitivity analysis showed consistent results, regardless of the model used (Figure 1, bottom). In the BMS-ISR group, the TIS (Treatment of In-Stent Restenosis) and PEPCAD II (The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to Treat In-Stent Restenoses) trials had higher relative weight, and a mild-to-moderate degree of heterogeneity ($I^2 = 37.8\%$), mainly driven by the RIBS V (Restenosis Intra-Stent of Bare-Metal Stents: Paclitaxel-Eluting Balloon vs Everolimus-Eluting Stent) trial effect, was detected. In the DES-ISR group, the ISAR-DESIRE 3 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches) trial had higher relative weight and no heterogeneity across effects was detectable ($I^2 = 0\%$).

PRIMARY SAFETY ENDPOINT. In BMS-ISR, the risk of all-cause death, myocardial infarction, or target lesion thrombosis did not significantly differ between DCB and DES (8.7% vs. 7.5%; HR: 1.13; 95% CI: 0.65 to 1.96). In DES-ISR, there was a borderline numerical trend toward a decreased risk after DCB angioplasty compared with DES implantation (9.5% vs. 13.3%; HR: 0.69; 95% CI: 0.47 to 1.00); no significant interaction was observed ($p_{interaction} = 0.146$) (Figure 2, top; Table 3).

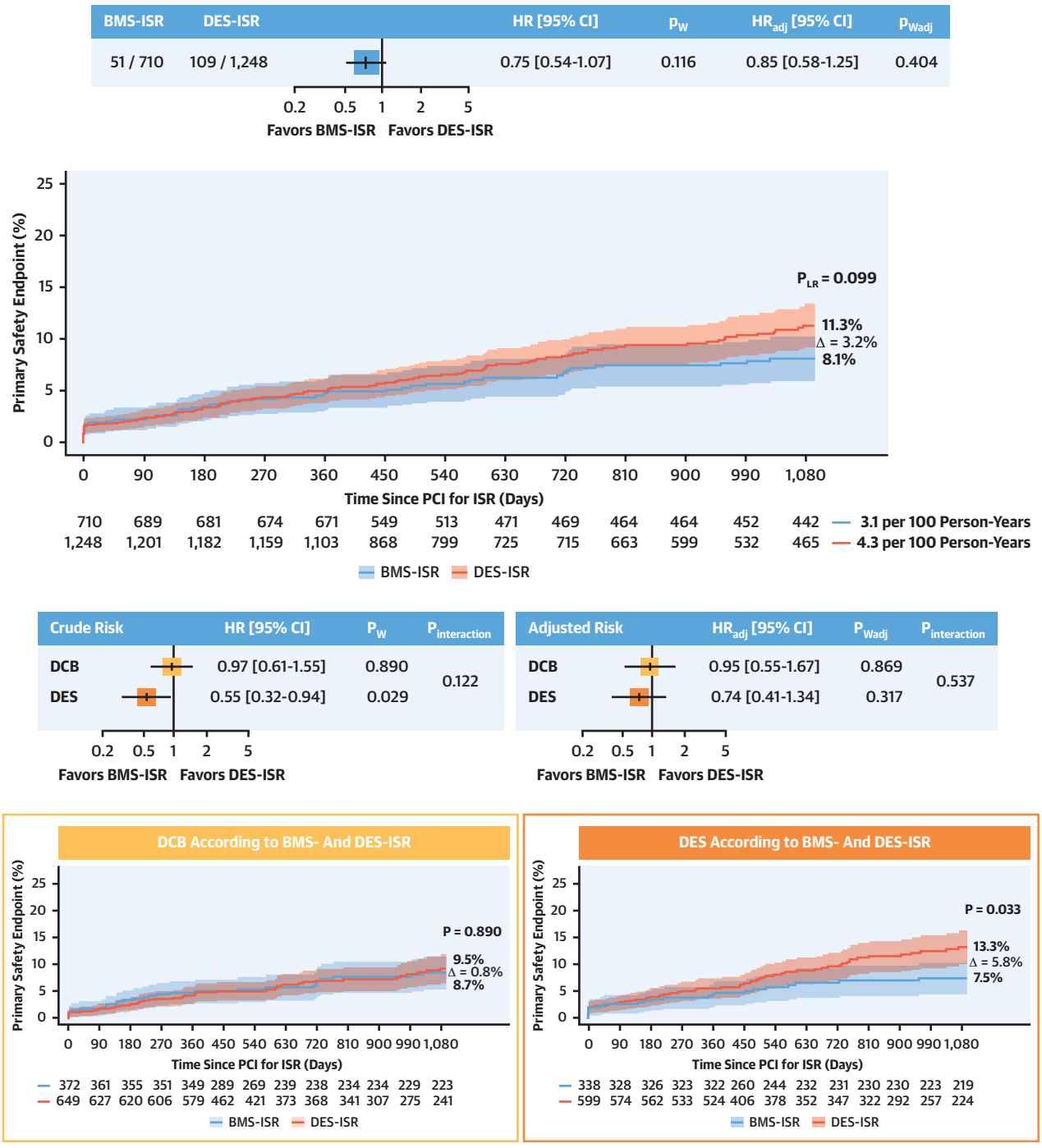
After multivariable adjustment, results remained not statistically significant (BMS-ISR: HR: 0.98; 95% CI: 0.53 to 1.82; DES-ISR: HR: 0.66; 95% CI: 0.43 to 1.03; $p_{interaction} = 0.308$) (Figure 2, Table 4).

The cumulative incidence of all-cause death, myocardial infarction, or target lesion thrombosis at 3-year follow-up was not significantly different across the 4 groups and was defined by the type of restenosed stent and allocated treatment ($p = 0.076$) (Figure 2, middle).

Two-stage sensitivity analysis showed consistent results, regardless of the model used (Figure 2, bottom). In the BMS-ISR group, the RIBS V, PEPCAD II, and TIS trials had higher relative weight, and no heterogeneity was detectable ($I^2 = 0\%$). In the DES-ISR group, the ISAR-DESIRE 3 and RIBS IV (Restenosis Intra-Stent of Drug-Eluting Stents: Paclitaxel-Eluting Balloon vs. Everolimus-Eluting Stent) trials had higher relative weight, and heterogeneity was low ($I^2 = 8.0\%$).

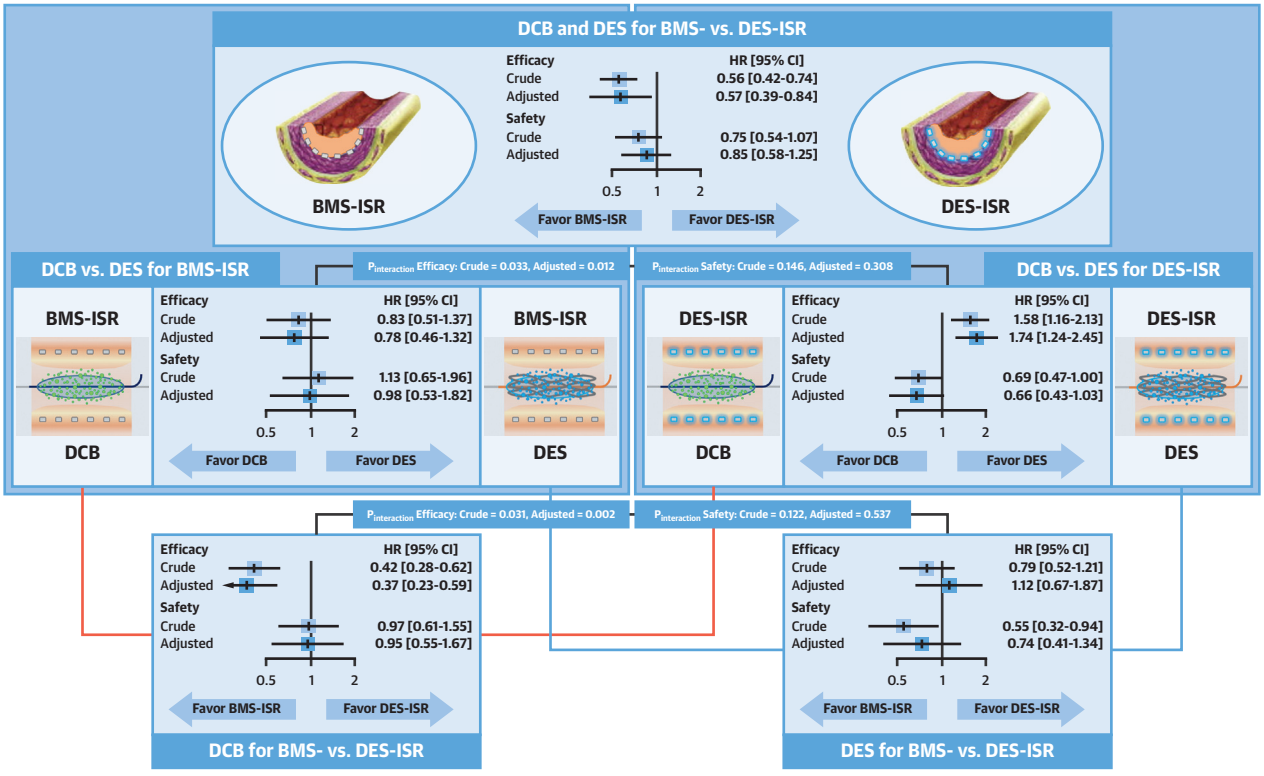
SECONDARY ENDPOINTS. The secondary endpoints at 3-year follow-up are displayed in Table 3. In BMS-ISR, no significant differences between DCB and DES for all the individual and composite secondary endpoints were observed. Results remained unchanged after multivariable adjustment (Table 4). Results by 2-stage analyses were consistent, and there was limited degree of heterogeneity across the endpoints (Supplemental Table 2). In DES-ISR, the difference in the risks of all-cause (HR: 0.61; 95% CI: 0.37 to 1.03) and cardiac death (HR: 0.46; 95% CI: 0.21 to 1.03) did not reach the formal threshold of significance. The risks of myocardial infarction (HR: 0.99; 95% CI: 0.58 to 1.70) and target lesion thrombosis (HR: 0.92; 95% CI: 0.30 to 2.86) were not significantly different between groups (Table 3). The risks of ischemia-driven TLR (HR: 1.67; 95% CI: 1.21 to 2.31) and target vessel revascularization (HR: 1.39; 95% CI: 1.05 to 1.84) were significantly lower after DES compared with DCB (Table 3). All the effects remained unchanged after multivariable adjustment (Table 4). Regardless of the model used, the 2-stage analyses produced consistent results with limited

FIGURE 4 BMS- Versus DES-ISR: Primary Safety Endpoint



(Top) Crude and multivariable-adjusted risk estimates between BMS- and DES-ISR are illustrated. **(Middle)** Distribution of the events over time by ISR type is illustrated by Kaplan-Meier analysis. Crude **(left)** and multivariable-adjusted **(right)** risk estimates for DCB **(yellow squares)** and DES **(orange squares)** according to BMS- versus DES-ISR are reported by forest plots. **(Bottom)** Distribution of the events over time for DCB **(left)** and DES **(right)** according to BMS- versus DES-ISR are illustrated by Kaplan-Meier analysis. Abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Efficacy and Safety of Drug-Coated Balloon Angioplasty and Drug-Eluting Stent Implantation According to In-Stent Restenosis Type**



Giacoppo, D. et al. J Am Coll Cardiol. 2020;75(21):2664-78.

(Top, center) Primary efficacy and safety endpoints risk estimates between in-stent restenosis (ISR) types, regardless of the treatment used. **(Middle)** Primary efficacy and safety endpoints risk estimates between drug-coated balloon (DCB) angioplasty and drug-eluting stent (DES) implantation for the treatment of bare-metal stent (BMS)-ISR **(left)** and DES-ISR **(right)**. The p values for treatment-by-subgroup interactions are reported. **(Bottom)** Device-specific risk estimates of primary efficacy and safety endpoints according to BMS- and DES-ISR. The p values for treatment-by-subgroup interactions are reported. BMS = bare-metal stent; CI = confidence interval; DCB = drug-coated balloon; DES = drug-eluting stent; HR = hazard ratio; ISR = in-stent restenosis; $p_{interaction}$ = p value of treatment-by-subgroup interaction test.

degree of heterogeneity across the endpoints (Supplemental Table 2).

BMS- VERSUS DES-ISR. Baseline characteristics between BMS- and DES-ISR groups are reported in Supplemental Table 3. Angiographic and procedural characteristics between BMS- and DES-ISR groups are reported in Supplemental Table 4.

At 3-year follow-up, the risk of TLR was significantly lower in patients who underwent PCI for BMS-ISR compared with those who underwent PCI for DES-ISR (9.7% vs. 17.0%; HR: 0.56; 95% CI: 0.42 to 0.74) (**Figure 3**, top; **Table 5**); after multivariable adjustment results did not change (HR_{adj}: 0.57; 95% CI: 0.39 to 0.84) (**Figure 3**, top; **Table 5**).

By comparing outcomes between BMS- and DES-ISR within patients assigned to one of the treatments, DCB was associated with a reduced risk of TLR in BMS-ISR (HR: 0.42; 95% CI: 0.28 to 0.62) (**Figure 3**, left forest plot), whereas DES did not show significant risk variations between ISR types (HR: 0.79; 95% CI: 0.52 to 1.21) (**Figure 3**, left forest plot), with a significant treatment-by-subgroup interaction ($p_{interaction}$ = 0.031); results were consistent after multivariable adjustment (**Figure 3**, right forest plot).

The risk of all-cause death, myocardial infarction, or target lesion thrombosis did not significantly differ between BMS- and DES-ISR (HR: 0.75; 95% CI: 0.54 to 1.07) (**Figure 4**, top; **Table 5**), without changes after multivariable adjustment (HR_{adj}: 0.85; 95% CI: 0.58 to 1.25) (**Figure 4**, top; **Table 5**).

By comparing outcomes between BMS- and DES-ISR within patients assigned to one of the treatments, safety outcomes after DCB did not show an influence of the ISR type (**Figure 4**, left forest plot), without changes

after multivariable adjustment (Figure 4, right forest plot). At crude analysis, a reduced risk of all-cause death, myocardial infarction, or target lesion thrombosis (HR: 0.55; 95% CI: 0.32 to 0.94) was associated with BMS-ISR in patients receiving DES (Figure 4, left forest plot). However, the effect became largely neutral after multivariable adjustment (HR_{adj}: 0.74; 95% CI: 0.41 to 1.34) (Figure 4, right forest plot) and interaction was not significant ($p_{interaction} = 0.122$).

No significant differences in individual safety endpoints were observed between ISR types, with consistent results after multivariable adjustment (Table 5). The risks of ischemia-driven TLR and target vessel revascularization were lower in BMS-ISR than in DES-ISR, but after multivariable adjustment only the first result was confirmed (Table 5).

DISCUSSION

The results of this analysis from the DAEDALUS study can be summarized as follows (Central Illustration):

- At 3-year follow-up, efficacy between DCB angioplasty and repeat stenting with DES for the treatment of coronary ISR is quite similar when the restenosed stent was a BMS, whereas repeat stenting with DES implantation outperforms DCB angioplasty when the restenosed stent was a DES.
- At 3-year follow-up, there are no statistically significant differences in the risk of all-cause death, myocardial infarction, or target lesion thrombosis between DCB and DES, both in BMS- and DES-ISR, though a numerical excess of events was detected after repeat DES implantation for DES-ISR.
- DES-ISR is associated with higher rates of TLR and ischemia-driven TLR compared with BMS-ISR, whereas differences in safety endpoints between settings are not significant.
- DES performance is not significantly affected by the type of restenotic stent, whereas anti-restenotic efficacy of DCB angioplasty is higher in BMS-ISR.
- Safety of DCB angioplasty does not seem to be significantly different between BMS- and DES-ISR, whereas a potential signal of harm associated with repeat DES implantation for DES-ISR at crude analysis was not supported by significant treatment-by-subgroup interaction and the effect became largely neutral after multivariable adjustment.

To the best of our knowledge, no direct comparison between DCB and DES according to BMS- and DES-ISR from randomized clinical trials and observational studies is available. The few previous reports limited the analyses to the assessment of differential efficacy and safety for each device, either DCB or DES, between BMS- and DES-ISR (18,30,31).

The DAEDALUS study shows for the first time in a large number of patients that DCB angioplasty and repeat stenting with DES have similar long-term efficacy in the treatment of BMS-ISR. This result may provide a rationale for using the device that avoids an additional permanent metallic layer, with possible advantages in terms of reiteration of the mechanisms leading to recurrent ISR and more flexible application of future treatments.

On the other hand, in patients with DES-ISR, repeat DES implantation has superior antirestenotic efficacy compared with DCB angioplasty. Indeed, patients treated by DES showed a 37% risk decrease in 3-year TLR compared with those treated with DCB. These observations may provide a rationale for preference of repeat stenting with DES in this setting.

With respect to the primary safety endpoint, previous studies have not provided definite answers about the safety of DCB and DES for the treatment of BMS- and DES-ISR. Moreover, the absence of significant differences in randomized clinical trials needs to be viewed in the context of the limited individual sample size (16,20,30,31). The DAEDALUS study shows no statistically significant differences between DCB and DES in all-cause death, myocardial infarction, or target lesion thrombosis in both BMS- and DES-ISR settings. However, whereas in BMS-ISR the margin of nonsignificance was very large, in DES-ISR there was a borderline numerical increase after repeat DES implantation compared with DCB angioplasty. It was reassuring that there was not significant treatment-by-subgroup interaction, and no significant difference between DCB and DES emerged after multivariable adjustment. Although the explanation for such effect requires further analyses and might be function of statistical power, it might also simply reflect an effect of chance.

Histopathology and endovascular imaging data have indicated differences in restenotic tissue characteristics between BMS- and DES-ISR (32–34). However, the clinical implications of the restenotic stent type on long-term outcomes after repeat PCI are less clear and underexplored (7).

The DAEDALUS study shows that treatment of DES-ISR is more challenging than treatment of BMS-ISR, due to higher rates of repeat revascularization. The 7.3% absolute difference in the 3-year incidence of TLR between BMS- and DES-ISR, regardless of the treatment by DCB or DES, highlights the magnitude of the effect.

However, the treatment-related influence might have had a role. Indeed, in our analysis, the risk of long-term TLR after DCB angioplasty was lower in BMS- than DES-ISR, whereas it did not significantly

differ between BMS- and DES-ISR after repeat stenting with DES. Our findings on the relative performance of DCB angioplasty according to the type of restenotic stent are consistent with previous reports. In an early, small, randomized trial comparing DCB with conventional balloon for the treatment of ISR, late lumen loss (0.05 ± 0.28 mm vs. 0.18 ± 0.38 mm; p = 0.03) and recurrent ISR (1.1% vs. 9.1%; p = 0.04) after DCB were lower in BMS-ISR than in DES-ISR setting (35). Later, a single-arm, observational study showed that 2-year TLR incidence after DCB angioplasty was lower in BMS- than DES-ISR (8.7% vs. 24.2%; p = 0.003) (22). Recently, a single-arm analysis from the RIBS IV and RIBS V trials confirmed higher rates of target vessel revascularization after DCB for DES-ISR compared with BMS-ISR (31). Conversely, previous findings about the relative performance of repeat stenting with DES according to the type of restenotic stent were mixed. Results from an all-comers observational post-marketing study of patients with ISR treated with DES have shown similar efficacy and safety between BMS- and DES-ISR (5). Steinberg et al. (20) matched 2 small groups of patients undergoing DES implantation, respectively, for BMS- and DES-ISR, and at 1-year follow-up, they observed lower rates of target vessel revascularization in the BMS-ISR group compared with DES-ISR group (10.3% vs. 22.2%; p = 0.01). In a pooled analysis from the ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis) and ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis 2) trials, results were contrasting within the DES category, with lower antirestenotic efficacy of sirolimus-DES implantation for sirolimus-DES-ISR compared with BMS-ISR and similar performance of paclitaxel-DES implantation between sirolimus-DES- and BMS-ISR settings (21). More recently, a single-arm analysis from the RIBS IV and RIBS V trials showed that the rate of target vessel revascularization after DES implantation for DES-ISR was higher compared with DES implantation for BMS-ISR (30).

In terms of explanation for these observations, it is known that exaggerated neointimal hyperplasia is among the major factors leading to ISR and the higher efficacy of DES over BMS for de novo coronary artery disease is primarily related to the mitigation of this phenomenon by elution of an antiproliferative medication (36,37). Accordingly, it might be reasonable to suppose that a substantial proportion of BMS-ISR lesions are still susceptible to the drug delivered by DCB angioplasty or DES implantation, whereas many DES-ISR lesions may be considered as an expression of the individual resistance to the antiproliferative therapy. These considerations fit with the observation in our study of similar incidences of TLR between DCB and DES in BMS-ISR, despite the differences in mechanical properties between devices. According to our findings, however, although in DES-ISR a drug-delivery-based approach might have lower efficacy in preventing recurrent stenosis, vessel scaffolding provided by repeat stenting with DES, compared with DCB angioplasty, might overcome this limitation in many patients, at least for the first years.

Finally, emerging evidence supports the role of neoatherosclerosis as a key component in the development of ISR (34,38). Differences between DCB angioplasty and DES implantation for the treatment of ISR may be also adduced to specific histopathologic and timing characteristics of neoatherosclerosis in the BMS- and DES-ISR subsets (34,38).

STUDY LIMITATIONS. The present study shares some of the limitations of the original trials, though the improvement of consistency across trials for several variables, the use of additional unpublished data that were available in the original databases, and the extension of the follow-up when possible significantly reduced the amount of heterogeneity (19). Specific additional limitations are as follows. First, although all trials were randomized, there were differences in the design with respect to BMS- or DES-ISR. Indeed, some trials included exclusively BMS- or DES-ISR, whereas others allowed both ISR types without balanced stratification. Notwithstanding, in the pooled dataset, only limited signs of imbalance in baseline characteristics were detected within the BMS- and DES-ISR subgroups according to DCB angioplasty or repeat stenting with DES. Second, in the analysis comparing BMS- with DES-ISR, regardless of the treatment used, restenotic lesion morphology significantly differed in line with well-known observations from previous studies (e.g., BMS-ISR more frequently was diffuse and DES-ISR more frequently was focal) (7). However, after multivariable adjustment including ISR angiographic pattern and lesion length, results overall did not change. Third, the heterogeneous assessment of dual antiplatelet and statin therapies status at very long-term follow-up across trials did not permit us to adjust the results also for these variables. Finally, it is known that multiple baseline clinical conditions can influence outcomes after PCI, especially in the challenging subset of ISR (7). However, the impact of this aspect on the results of our study is deemed to be low because after nonparsimonious multivariable adjustment results remained consistent.

CONCLUSIONS

In patients with BMS-ISR, DCB angioplasty and repeat stenting with DES are similarly effective and safe at long-term follow-up. In patients with DES-ISR, repeat DES implantation is significantly more effective and apparently similarly safe compared with DCB angioplasty at long-term follow-up. Overall, compared with BMS-ISR, DES-ISR is associated with higher rates of target lesion revascularization.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with in-stent restenosis (ISR) of a bare-metal coronary stent, drug-coated balloon (DCB) angioplasty and drug-eluting stent (DES) implantation are associated with similar long-term efficacy and safety, whereas in patients with ISR of a coronary DES repeat DES implantation is more efficacious than DCB angioplasty and similarly safe.

TRANSLATIONAL OUTLOOK: Further investigation is needed to define clinical and angiographic subsets leading to greater or lesser efficacy between these alternative strategies of repeat coronary revascularization.

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KEY WORDS drug-coated balloon, drug-eluting stent, individual patient data, in-stent restenosis, percutaneous coronary intervention, randomized clinical trial, restenosis

APPENDIX For supplemental figures, tables, search methods, and a list of the trials included in DAEDALUS study, please see the online version of this paper.