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)

Daniele Giacoppo1, Fernando Alfonso2, Bo Xu3, Bimmer E.P.M. Claessen4, Tom Adriaenssens5, Christoph Jensen6, María J. Pérez-Vizcaíno7, Do-Yoon Kang8, Ralf Degenhardt9, Leos Pleva10, Jan Baan11, Javier Cuesta2, Duk-Woo Park8, Heribert Schunkert1,12, Roisin Colleran1, Pavel Kukla10, Pilar Jiménez-Quevedo7, Martin Unverdorben9,13, Runlin Gao3, Christoph K. Naber6, Seung-Jung Park8, José P.S. Henriques11, Adnan Kastrati1,12, and Robert A. Byrne1,12*

1Department of Cardiovascular Diseases, Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany; 2Department of Cardiology, Hospital Universitario de La Princesa Madrid, Calle Diego de León 62, Madrid 28006, Spain; 3Department of Cardiology, Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, 167 Beilishi Road, Xicheng, 100037 Beijing, China; 4Mount Sinai Heart, the Zena and Michael Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, 1428 Madison Avenue, 10029 New York, NY, USA; 5Department of Cardiovascular Diseases, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium; 6Department of Cardiology, Contilia Heart and Vascular Center, Elisabeth Krankenhaus, Clara-Kopp-Weg 1, 45138 Essen, Germany; 7Department of Cardiology, Hospital Clinico San Carlos, Calle Professor Martin Lagos, 28040 Madrid, Spain; 8Department of Cardiology, Asan Medical Center, University of Ulsan, 388-1 Poongnapdong, Seoul 138-736, South Korea; 9Department of Cardiology, Herz-Kreislauf-Zentrum, Heinz-Meise-Strasse 100, 36199 Rotenburg an der Fulda, Germany; 10Department of Cardiology, University Hospital Ostrava, tr. 17 listopadu 1790, 70852 Ostrava, Czech Republic; 11Department of Cardiology, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 Amsterdam, the Netherlands; 12DZHK (German Centre for Cardiovascular Research), Munich Heart Alliance, Marchioninistrasse 15, 81377 Munich, Germany; and 13Daiichi Sankyo, 211 Mt. Airy Road, 07920 Basking Ridge, NJ, USA

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...
In stent restenosis (ISR) represents the most common cause of treatment failure after percutaneous coronary intervention. 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.

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. 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 point. In addition, bare-metal stents continue to be used occasionally and are associated with high rates of ISR.

Several therapies for coronary ISR have been tested in clinical trials. However, paclitaxel-coated balloon (PCB) angioplasty and repeat stenting with DES implantation have emerged as the most effective therapeutic options. 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. 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.

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.

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

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) 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 (#K52017-Z36).
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 $\chi^2$ 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 confidence intervals and numbers at risk, and comparisons performed by the log rank test.15–17 For each outcome, primary results were with 95% confidence intervals and numbers at risk, and comparisons per-

### 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-exci-

### 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 (HRadj) 1.38, 95% CI 1.05–1.82, $P = 0.020$].
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 ($\chi^2 = 0.080; I^2 = 44.3\%$).

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 1 Main characteristics of the included randomized clinical trials

| Trial          | Design | Centres | Region   | Investigation time | Patients (lesions) Total | PCB type | DES type | Restenotic stent |
|----------------|--------|---------|----------|-------------------|--------------------------|----------|----------|------------------|
| PEPCAD II     | 1:1    | 10      | Germany  | Jan 2006          | 131 (131)                | 3 μg/mm² | Iopromide| Bare-metal       |
| Core lab      | Open-Label | Core lab | Dec 2006 |                  | 66 (66) 65 (65)         |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |
| ISAR DESIRE 3 | 1:1    | 3       | Germany  | Aug 2009          | 268 (340)                | 3 μg/mm² | Iopromide| Bare-metal       |
| Core lab      | Open-Label | Core lab | Oct 2011 |                  | 137 (172) 131 (168)     |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |
| PEPCAD China ISR | 1:1 | 17      | China    | Mar 2011          | 215 (221)                | 3 μg/mm² | Iopromide| Drug-eluting     |
| Core lab      | Open-Label | Core lab | Apr 2012 |                  | 109 (113) 106 (108)     |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |
| RIBS V        | 1:1    | 25      | Spain    | Jan 2010          | 189 (189)                | 3 μg/mm² | Iopromide| Bare-metal       |
| Core lab      | Open-Label | Core lab | Jan 2012 |                  | 95 (95) 94 (94)         |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |
| SEDUCE        | 1:1    | 2       | Belgium  | Jun 2009          | 49 (49)                  | 3 μg/mm² | Iopromide| Bare-metal       |
| Core lab      | Open-Label | Core lab | Oct 2011 |                  | 24 (24) 25 (25)         |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |
| RIBS IV       | 1:1    | 23      | Spain    | Jan 2010          | 309 (309)                | 3 μg/mm² | Iopromide| Drug-eluting     |
| Core lab      | Open-Label | Core lab | Aug 2013 |                  | 154 (154) 155 (155)     |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |
| TIS           | 1:1    | 1       | Czech    | Jan 2012          | 136 (148)                | 3 μg/mm² | Iopromide| Bare-metal       |
| Core lab      | Open-Label | Core lab | Aug 2014 |                  | 68 (74) 68 (74)         |          |           |                  |
|               | CEC    |         | Republic |          |                          |          |           |                  |
| DARE          | 1:1    | 8       | Netherlands | May 2010 |                 | 278 (278) | 3 μg/mm² | Everolimus-eluting |
| Core lab      | Open-Label | Core lab | Jun 2015 |                  | 137 (137) 141 (141)     |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |
| RESTORE       | 1:1    | 10      | South Korea | Apr 2013 |                | 172 (172) | 3 μg/mm² | Everolimus-eluting |
| Core lab      | Open-Label | Core lab | Oct 2016 |                  | 86 (86) 86 (86)         |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |
| BOLLUX-RCT    | 2:1    | 14      | Germany, Latvia | Aug 2012 |            | 229 (243) | 3 μg/mm² | Sirolimus-eluting |
| Core lab      | Open-Label | Core lab | Jan 2015 |                  | 157 (163) 72 (80)       |          |           |                  |
|               | CEC    |         |          |                   |                          |          |           |                  |

BTHC, butyryl-tri-hexyl citrate; CEC, clinical events committee.
### 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.
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 (HRadj 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 0.80, 95% CI 0.58–1.10, P = 0.160) (Figure 3). The highest relative weights were associated with the ISAR-DESIRE 3, RIBS IV, BIOLOX-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 (HRadj 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 (HRadj 1.08, 95% CI 0.58–2.08, P = 0.774) (Figure 5).
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
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
relatively small difference between the two treatments against an intermediate degree of between-trial heterogeneity. 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. 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.

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.
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. 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 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.

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). 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; HRadj, adjusted hazard ratio; PCB, paclitaxel-coated balloon. The numbers of patients at risk in the treatment groups are shown below the graphs.
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. Fourth, the interesting findings emerging from subgroup analyses need to be interpreted bearing in mind the reduced statistical power after grouping. 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.

![Diagram](image)

**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. Primary efficacy endpoint was target lesion revascularization; primary safety endpoint was the composite of death, myocardial infarction, or target lesion thrombosis; net composite endpoint 1 refers to the composite of death, myocardial infarction, target lesion thrombosis, or target lesion revascularization; net composite endpoint 2 refers to the composite of death, myocardial infarction, target lesion thrombosis, or target vessel revascularization.
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 Scientific and Micell Technologies, and research funding to the institution. F.D.G. reports research grant from the European Union. "Supporting information submitted with the manuscript.

References

1. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. Eur Heart J. 2015;36:3320–3331.

2. Cassese S, Byrne RA, Schulz S, Hopmann P, Kreutzer J, Feuchtenberger A, Ibrahim T, Ott I, Fusaro M, Schunkert H, Laugwitz KL, Kastrati A. Prognostic role of restenosis in 10004 patients undergoing routine control angiography after coronary stenting. Eur Heart J. 2015;36:94–99.

3. Farooq V, Gogas BD, Serruys PW. Restenosis: delineating the numerous causes of drug-eluting stent restenosis. Circ Cardiovasc Interv. 2011;4:195–205.

4. Iqbal J, Serruys PW, Silber S, Kelbaek H, Richardt G, Morel MA, Negoita M, Buus P, Windecker S. Comparison of zotarolimus- and everolimus-eluting coronary stents: final 5-year report of the RESOLUTE all-comers trial. Circ Cardiovasc Interv. 2015;8:e002230.

5. Vlahajannis GJ, Smits PC, Hofma SH, Togni M, Vazquez N, Valdes M, Voudris V, Slagboom T, Goy JJ, den Heijer P, van der Ent M. Biodegradable polymer biolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with coronary artery disease: five-year results from the COMPARE II Trial. JACC Cardiovasc Interv. 2017;10:1215–1221.

6. Kufner S, Joner M, Thannheimer A, Hopmann P, Ibrahim T, Mayer K, Cassese S, Laugwitz KL, Schunkert H, Kastrati A, Byrne RA. Ten-year clinical outcomes from a trial of three limus-eluting stents with different polymer coatings in patients with coronary artery disease: results from the ISAR-TEST 4 randomized trial. Circulation. 2019;139:325–333.

7. Colombo A, Giannini F, Briguori C. Should we still have bare-metal stents available in our catheterization laboratory? J Am Coll Cardiol. 2017;70:607–619.

8. Cassese S, Byrne RA, Tada T, Pinieck S, Joner M, Ibrahim T, King LA, Fusaro M, Laugwitz KL, Kastrati A. Incidence and predictors of restenosis after coronary stenting in 10004 patients with surveillance angiography. Heart. 2014;100:153–159.

9. Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. J Am Coll Cardiol. 2014;63:2659–2673.

10. Giacoppo D, Garribio G, Aruta P, Capranzano P, Tambrunino C, Capodanno D. Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4808 patients. BMJ. 2015;351:h5392.

11. Sintis GC, Stefanini GG, Mavridis D, Sintis KC, Alfonso F, Perez-Vizcaíno MJ, Byrne RA, Kastrati A, Meier B, Salanti G, Juni P, Windecker S. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. Lancet. 2015;386:655–664.

12. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2018;7:e011245.

13. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF. Preferred Reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA. 2015;313:1657–1665.

14. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van ES GA, Steg PG, Morice MA, Mauri L, Virmani R, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115:2344–2351.

15. Theureau TM, Grambsch PM. Modeling Survival Data: extending the Cox Model. New York: Springer; 2000.

16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457–481.

17. Aalen O, Borgan Ø, Gjessing H. Survival and Event History Analysis. New York: Springer; 2008.

18. Bowden J, Tierney JF, Simmonds M, Copas AJ, Higgins JP. Individual patient data meta-analysis of time-to-event outcomes: one-stage versus two-stage approaches for estimating the hazard ratio under a random effects model. Res Synth Meth. 2011;2:150–162.

19. Debray TP, Moons K, van Valkenhoef G, Eeftinck H, Hummel N, Groenewold RH, Retama JR. Get real in individual participant data (IPD) meta-analysis: a view of the methodology. Res Synth Meth. 2015;6:293–309.

20. Altman DG. Calculating the number needed to treat for trials where the outcome is a time event. BMJ. 1999;319:1492–1495.

21. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in r. J Stat Soft 2011;45:1–67.

22. Borenstein M. Introduction to Meta-Analysis. Chichester: John Wiley & Sons; 2009.

23. Schriger DL, Altman DG, Vetto JA, Heafner T, Mohler D. Forest plots in reports of systematic reviews: a cross-sectional study reviewing current practice. Int J Epidemiol. 2010;39:421–429.

24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–560.

25. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.10. 2011. https://handbook-5-1.cochrane.org/ (15 May 2019).

26. Schünemann H, Brazech J, Guyatt G, Oxman A. Handbook for Grading the Quality of Evidence and the Strength of Recommendations Using the GRADE Approach. https://gdt.gradepro.org/app/handbook/handbook.html (15 May 2019).

27. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, Werner G, Antoni D, Kleber FX, Bocksch W, Leschke M, Ackermann H, Bockberger M, Speck U, Degenhardt R, Scheller B. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation. 2009;119:2986–2994.

28. Byrne RA, Neumann FJ, Mahrholdt H, Mahli J, Pinieck S, Wolff B, Tiroch K, Schulz S, Fusaro M, Ott I, Ibrahim T, Hausleiter J, Valina C, Pache J, Laugwitz KL, Massberg S, Kastrati A. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet. 2013;381:461–467.

29. Xu B, Gao R, Wang J, Yang Y, Chen S, Liu B, Chen F, Li Z, Han Y, Fu G, Zhao Y, Ge J. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. JACC Cardiovas Interv. 2014;7:204–211.

30. Alfonso F, Pérez-Vizcaíno MJ, Cárdenas A, Garcia del Blanco B, Seidenberger B, Iaquinta A, Gómez-Rejano M, Masotti M, Velázquez MT, Sanchez J, Garcia-Touchar A, Zueco J, Bethencourt A, Melgares R, Ceguer A, Domínguez M, Mainar V, López-Minguez JR, More J, Martí V, Moreno R, Jiménez-Quevedo P, Gonzalo N, Fernández C, Macaya C. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V clinical trial. J Am Coll Cardiol. 2016;63:1378–1386.

31. Adriaensen T, Dens J, Ugli B, Bennett J, Dubois C, Sinnaeve P, Wiyono S, Coosemans M, Belmans A, D’hooge J, Vrolix M, Desmet W. Optical coherence tomography study of healing characteristics of paclitaxel-eluting balloons versus everolimus-eluting stents for in-stent restenosis: the SEDUCE randomised clinical trial. EuroIntervention. 2014;10:439–448.

32. Alfonso F, Pérez-Vizcaíno MJ, Cárdenas A, García del Blanco B, García-Touchar A, López-Minguez JR, Benedito A, Masotti M, Zueco J, Iaquinta A, Velázquez M, Moreno R, Mainar V, Domínguez A, Pomar F, Melgares R, Rivero F, Jiménez-Quevedo P, Gonzalo N, Fernández C, Macaya C. A prospective...
randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV randomized clinical trial. J Am Coll Cardiol 2015;66:23–33.

33. Pleva L, Kukla P, Kusnerova P, Zapletalova J, Hlinomaz O. Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis: the treatment of in-stent restenosis study. Circ Cardiovasc Interv 2016;9:e003316.

34. Baan J, Claessen BE, Dijk K, B-V, Vendrik J, van der Schaaf RJ, Meuwissen M, van Royen RJ, Koch KT, Sjauw KD, Beijk MA, Vis MM, Wykrzykowska JJ, Piek JJ, Tijssen JGP, Henriques JPS. A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: the DARE trial. JACC Cardiovasc Interv 2018;11:275–283.

35. Wong YTA, Kang DY, Lee JB, Rha SW, Hong YJ, Shin ES, Her SH, Nam CW, Chung WY, Kim MH, Lee CH, Lee PH, Ahn JM, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park DW, Park SJ. Comparison of drug-eluting stents and drug-coated balloon for the treatment of drug-eluting coronary stent restenosis: a randomized RESTORE trial. Am Heart J 2018;197:35–42.

36. Jensen CJ, Richardt G, Tölz R, Erglis A, Sturk C, Jung W, Neumann FJ, Stangl K, Brachmann J, Fischer D, Mehli J, Rieber J, Wiemer M, Schofer J, Sack S, Naber CK. Angiographic and clinical performance of a paclitaxel-coated balloon compared to a second-generation sirolimus-eluting stent in patients with in-stent restenosis: the BIO-LUX randomised controlled trial. EuroInterv 2018;14:1096–1103.

37. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. Stat Med 2017;36:855–875.

38. Byrne RA, Joner M, Tada T, Kastrati A. Restenosis in bare metal and drug-eluting stents: distinct mechanistic insights from histopathology and optical intravascular imaging. Minerva Cardioangiolog 2012;60:473–489.

39. Byrne RA, Cassese S, Windsch T, King LA, Joner M, Tada T, Mehli JJ, Pache J, Kastrati A. Differential relative efficacy between drug-eluting stents in patients with bare metal and drug-eluting stent restenosis: evidence in support of drug-resistance: insights from the ISAR-DESIRE and ISAR-DESIRE 2 trials. EuroInterv 2013;9:797–802.

40. Neumann FJ, Sousa-Uva M, Ahlson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juní P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.

41. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)-uses of baseline data in clinical trials. Lancet 2000;355:1064–1069.

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.

© The Author(s) 2019. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com