JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 9, 2020

PUBLISHED BY ELSEVIER

Survival After Coronary Revascularization With Paclitaxel-Coated Balloons

Bruno Scheller, MD,[a,b] Davor Vukadinovic, MD,[a] Raban Jeger, MD,[c] Tuomas T. Rissanen, MD,[d] Sean S. Scholz, MD,[a] Robert Byrne, MD,[e] Franz X. Kleber, MD,[f] Azeem Latib, MD,[g] Yvonne P. Clever, MD,[a] Sebastian Ewen, MD,[a] Michael Böhm, MD,[a] Yiping Yang, PhD,[h] Alexandra Lansky, MD,[h] Felix Mahfoud, MD[a]

ABSTRACT

BACKGROUND Drug-coated balloons (DCBs) are accepted treatment strategies for coronary in-stent restenosis and are under clinical investigation for lesions without prior stent implantation. A recently published meta-analysis suggested an increased risk of death associated with the use of paclitaxel-coated devices in the superficial femoral artery. The reasons are incompletely understood as potential underlying pathomechanisms remain elusive, and no relationship to the administered dose has been documented.

OBJECTIVES The purpose of this analysis was to investigate the available data on survival after coronary intervention with paclitaxel-coated balloons from randomized controlled trials (RCTs).

METHODS PubMed, Web of science, and the Cochrane library database were searched, and a meta-analysis from RCT was performed comparing DCB with non-DCB devices (such as conventional balloon angioplasty, bare-metal stents, or drug-eluting stents) for the treatment of coronary in-stent restenosis or de novo lesions. The primary outcome was all-cause death. The number of patients lost to follow-up was observed at different time points. Risk estimates are reported as risk ratios (RRs) with 95% confidence intervals (CIs).

RESULTS A total of 4,590 patients enrolled in 26 RCTs published between 2006 and 2019 were analyzed. At follow-up of 6 to 12 months, no significant difference in all-cause mortality was found, however, with numerically lower rates after DCB treatment (RR: 0.74; 95% CI: 0.51 to 1.08; $p = 0.116$). Risk of death at 2 years ($n = 1,477$, 8 RCTs) was similar between the 2 groups (RR: 0.84; 95% CI: 0.51 to 1.37; $p = 0.478$). After 3 years of follow-up ($n = 1,775$, 9 RCTs), all-cause mortality was significantly lower in the DCB group when compared with control treatment (RR: 0.73; 95% CI: 0.53 to 1.00; $p = 0.047$) with a number needed to treat of 36 to prevent 1 death. A similar reduction was seen in cardiac mortality (RR: 0.53; 95% CI: 0.33 to 0.85; $p = 0.009$).

CONCLUSIONS In this meta-analysis, the use of paclitaxel DCBs for treatment of coronary artery disease was not associated with increased mortality, as has been suggested for peripheral arteries. On the contrary, use of coronary paclitaxel-coated balloons was associated with a trend toward lower mortality when compared with control treatments. (J Am Coll Cardiol 2020;75:1017–28) © 2020 by the American College of Cardiology Foundation.

From the [a]Internal Medicine III-Cardiology, Angiology and Intensive Care Medicine, Saarland University Hospital, Saarland University, Homburg/Saar, Germany; [b]Clinical and Experimental Interventional Cardiology, University of Saarland, Homburg/Saar, Germany; [c]University Hospital Basel, University of Basel, Basel, Switzerland; [d]Heart Center, North Karelia Central Hospital, Siun Sote, Joensuu, Finland; [e]Department of Cardiology, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; [f]Evangelisches Krankenhaus Paul Gerhardt Stift, Paul-Gerhardt-Straße 42-45, Lutherstadt Wittenberg, Germany; [g]Montefiore Medical Center, New York, New York; and the [h]Section of Cardiology, Yale University School of Medicine, New Haven, Connecticut. Dr. Scheller is a shareholder of InnoRa GmbH; and has been named as a coinventor on patent applications submitted by Charité University Hospital. Dr. Jeger has received research grant support and speaker honoraria from B.Braun; and has received speaker honoraria from Cardionovum. Dr. Rissanen has received research grant support and speaker honoraria from B.Braun. Dr. Scholz has received speaker honoraria from Pfizer. Dr. Byrne has received speaker fees from B. Braun, Melsungen AG, and Biotronik. Dr. Kleber has served as a consultant for and received speaker honoraria from B.Braun. Dr. Latib has served on the Advisory Board for Medtronic. Dr. Böhm has received support from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic, Servier, and Vifor. Dr. Mahfoud is supported by Deutsche Gesellschaft für Kardiologie (DGK) and Deutsche Forschungsgemeinschaft (SFB TRR219); and has received research grants/honoraria from Berlin Chemie, Boehringer Ingelheim, Medtronic, and Recor. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 25, 2019; revised manuscript received November 14, 2019, accepted November 24, 2019.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.11.065

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent

CAD = coronary artery disease

DCB = drug-coated balloon

DES = drug-eluting stent(s)

PAD = peripheral artery disease

PES = paclitaxel-eluting stent(s)

POBA = plain old balloon angioplasty

RCT = randomized controlled clinical trial

Drug-eluting stents (DES) are considered the therapy of choice for interventional treatment of coronary artery disease (CAD) (1). The performance of new-generation DES is characterized by favorable acute and subacute occlusion rates and low risk of restenosis. However, even with latest-generation DES, the annual event rate attributable to the device remains as high as 2%, which remains unchanged over time (2). To address this potential long-term risk, several concepts and approaches for avoiding permanent implants have been investigated. Among these, fully bioresorbable stents led to an unacceptable increased rate of stent thrombosis and myocardial infarction in the first years after implantation when compared with metallic DES, and are currently not considered a safe alternative (3).

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Drug-coated balloons (DCBs) combine the principle of angioplasty alone with local drug delivery. They are accepted for the treatment of coronary in-stent restenosis (1) and are under clinical investigation for coronary lesions without prior stent implantation (4,5). The available clinical evidence refers almost exclusively to paclitaxel-coated DCB. In peripheral artery disease (PAD), DCB were about to become the standard therapy for the transfemoral region. However, a meta-analysis published in December 2018 reported an increased mortality in trials with 2 or more years of follow-up after combining treatments with paclitaxel-coated stents or balloons in peripheral artery disease (6). The reasons for these findings are incompletely understood, as a potential underlying pathomechanism remains elusive and no relationship to the administered dose has been documented (7). Although the meta-analysis in peripheral arteries has considerable limitations (6), it has led to major uncertainty in the clinical community and raised questions about the safety of paclitaxel application in PAD. In the current situation concerning the peripheral vessels, a patient-level meta-analysis including patients from 4 randomized trials revealed no significant difference from all-cause death at 2 years (8). Furthermore, a Medicare analysis including 16,650 patients did not confirm any mortality signal created by paclitaxel-coated devices (9).

Theoretically, the avoidance of permanent metallic implants in coronary arteries could improve long-term survival. Some coronary studies indicate better survival for DCB-treated patients beyond the first year (5,10,11). Hence, none of these coronary studies were powered to assess the risk of long-term mortality appropriately. The present meta-analysis aims to investigate available survival data after coronary intervention exclusively with paclitaxel DCB from randomized controlled trials (RCTs).

METHODS

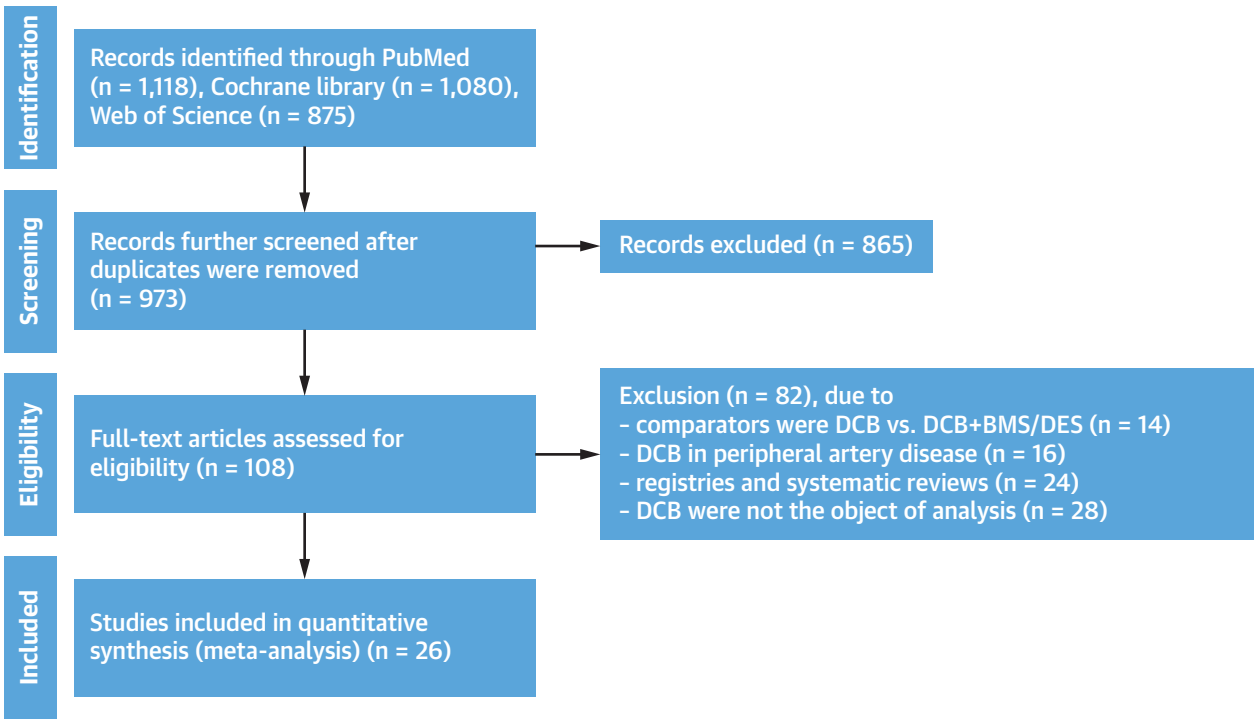
This analysis was performed following the recommendations for conducting and reporting meta-analyses from the PRISMA statement (12) and scientific statement from the American Heart Association (13).

STUDY PROTOCOL. The study was carried out according to a pre-defined protocol, submitted to the international PROSPERO database for prospective systematic reviews (PROSPERO 2019 CRD42019141127). Eligible trials had to be randomized, analyzing percutaneous coronary intervention with paclitaxel-coated balloon (without stent implantation) versus implantation of bare-metal stents (BMS) and/or drug-eluting stents (DES) or plain old balloon angioplasty (POBA) in different clinical settings (patients with acute coronary syndrome, stable angina pectoris, treatment of in-stent restenosis, and small vessel disease). The minimum duration of follow-up was ≥6 months. There were no limitations regarding number of enrolled patients. Most of the trials reported the number of events in all-cause mortality. When all-cause mortality was not reported, the rate of cardiac mortality was used instead (i.e., the Biolux RCT trial) (14).

We excluded trials that analyzed intervention with paclitaxel-coated balloons in patients for PAD or treatment of dysfunctional hemodialysis arteriovenous fistulas. Observational studies and registries as well as RCTs that explored comparison of coronary intervention with paclitaxel-coated balloon versus combined intervention, such as implantation of BMS or DES in addition to paclitaxel-coated balloon, were also excluded.

Data sources and search strategy. The PubMed, Web of science, and Cochrane library database were searched for eligible studies published from 2006 until August 2019. The PubMed search was performed using the following terms: “drug eluting balloon” OR “drug coated balloon” AND “randomized trial,” with additional activated filters: 1) article type (clinical trial, controlled clinical trial, review); 2) text availability (abstract, free full text, full text); and 3) publications dates (from January 1, 2006, to July 31, 2019). The detailed search strategy is shown in **Figure 1**.

FIGURE 1 PRISMA Flow Diagram



Flow of citations reviewed: number of records identified, included and excluded, and the reasons for exclusions. BMS = bare-metal stent; DCB = drug-coated balloon; DES = drug-eluting stent; POBA = plain old balloon angioplasty; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Selection process and data extraction. Two investigators (D.V. and S.S.S.) independently reviewed the search results for eligibility criteria according to their titles and abstracts, screened potentially eligible full-text papers considered for inclusion, and extracted the data for appropriate fields and endpoints from selected studies. The final decision concerning inclusion of studies in the analysis was done after consultation with a third investigator (B.S.). Corresponding authors or principal investigators of some of the included studies (BASKET SMALL 2 [Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions] [4], BELLO [Balloon Elution and Late Loss Optimization] [15], DEBUT [Drug-Coated Balloon for Treatment of De-Novo Coronary Artery Lesions in Patients with High Bleeding Risk] [5], Gobić STEMI [16], PATENT C [Paclitaxel-Coated Scoring Balloon vs. a Standard Balloon for Treatment of Coronary In-Stent Restenosis] [17], PEPCAD II [Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to Treat In-Stent Restenoses] [18], PEPCAD NSTEMI [Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease for Treatment of Non-ST-Elevation Myocardial Infarction] [19]) were contacted for review of conflicting or missing data. The following items were extracted from the included studies: comparators (paclitaxel-coated balloon, POBA, BMS, or DES), patient's number, primary outcome, indication for PCI (acute coronary syndrome, stabile angina pectoris, small vessel disease, in-stent restenosis [ISR]), duration of follow-up, registration number, and definition of mortality.

ASSESSMENT OF STUDY QUALITY. Each of the included studies was independently assessed for quality by 2 investigators (D.V. and B.S.) according to the Jadad score (20), which exhibits a low interobserver variability and is therefore recommended by the American Heart Association (13). Jadad score accounts for randomization (no randomization 0, randomization 1, data confirming appropriate randomization 2), blinding (no blinding 0, blinding 1, and data confirming appropriate blinding 2), and loss to follow-up (not reported 0, reported 1). Scores ≥3 represent high-quality studies, and studies with a score of 2 or less are considered low-quality studies.

STATISTICAL ANALYSIS. The primary outcome was all-cause mortality and was compared for patients

TABLE 1 Randomized Clinical Trials Included in the Meta-Analysis

Trial or First Author (Ref. #)	Indication	Groups	DCB, n	Control, n	Max FU	Primary Endpoint	Definition of Death	Study Registration
BASKET SMALL 2 (4)	SVD	SeQuent Please vs. PES/EES	382	376	12 months	MACE	All-cause	NCT01574534
BELLO (15,44,45)	SVD	In.Pact Falcon vs. PES	90	92	3 yrs	LLL	All-cause	NCT01086579
Biolux RCT (14)	ISR	Pantera Lux vs. SES	157	72	18 months	LLL, TLF	Cardiac	NCT01651390
DARE (21)	ISR	SeQuent Please vs. EES	137	141	12 months	MLD	All-cause	NTR2189
DEBUT (5)	HBR	SeQuent Please vs. BMS	102	106	3 yrs	MACE	All-cause	NCT01781546
Gobić et al. (16)	STEMI	SeQuent Please vs. SES	38	37	6 months	MACE, LLL	All-cause	–
Habara et al. (22)	ISR	SeQuent Please vs. POBA	25	25	8 months	LLL	All-cause	–
ISAR DESIRE III (10,23)	ISR	SeQuent Please vs. POBA vs. PES	137	134 131	3 yrs	Diameter stenosis	All-cause	NCT00987324
Nishiyama et al. (24)	De novo	SeQuent Please vs. EES	27	33	8 months	TLR, LLL	All-cause	–
Paccocath ISR (40–42)	ISR	Paccocath vs. POBA	54	54	5 yrs	LLL	All-cause	NCT00106587 NCT00409981
PATENT C (17)	ISR	AngioSculptX vs. AngioSculpt	33	28	2 yrs	LLL	All-cause	NCT01495533
PEPCAD BIF (25)	SB BIF	SeQuent Please vs. POBA	32	32	9 months	LLL	All-cause	NCT01180517
PEPCAD China ISR (11,26)	ISR	SeQuent Please vs. PES	110	110	2 yrs	LLL	All-cause	NCT01622075
PEPCAD DES (27,28)	ISR	SeQuent Please vs. POBA	72	38	3 yrs	LLL	All-cause	NCT00998439
PEPCAD II (18,29)	ISR	SeQuent Please vs. PES	66	65	3 yrs	LLL	All-cause	NCT00393315
PEPCAD NSTEMI (19)	NSTEMI	SeQuent Please vs. BMS/DES	104	106	9 months	TLF	All-cause	NCT01489449
PEPCAD JAPAN SVD (30)	SVD	SeQuent Please vs. POBA	92	41	6 months	LLL	All-cause	–
PICCOLETO (46)	SVD	Dior vs. PES	28	29	9 months	Diameter stenosis	All-cause	EudraCT 2009-012268-15
Restore China SVD (47)	SVD	Restore vs. ZES	116	114	9 months	Diameter stenosis	All-cause	NCT02946307
Restore Korea (31)	ISR	SeQuent Please vs. EES	86	86	12 months	LLL	All-cause	NCT01967199
Revelation (43)	STEMI	Pantera Lux vs. SES	60	60	9 months	FFR	All-cause	NCT02219802
RIBS IV (32,33)	ISR	SeQuent Please vs. EES	154	155	3 yrs	MLD	All-cause	NCT01239940
RIBS V (34,35)	ISR	SeQuent Please vs. EES	95	94	3 yrs	MLD	All-cause	NCT01239953
SEDUCE (36)	ISR	SeQuent Please vs. EES	25	25	12 months	OCT	All-cause	NCT01065532
Shin et al. (37)	De novo	SeQuent Please vs. EES	44	22	12 months	LLL	All-cause	–
TIS (38,39)	ISR	SeQuent Please vs. EES	68	68	3 yrs	LLL	All-cause	NCT01735825

Drug-coated balloons investigated: SeQuent Please (B.Braun, Melsungen, Germany), In.Pact Falcon (Medtronic, Galway, Ireland), Pantera Lux (Biotronik, Berlin, Germany), Paccocath (Bayer-Schering, Berlin, Germany), AngioSculptX (Phillips, Amsterdam, the Netherlands), Dior (Eurocor, Bonn, Germany), and Restore (Cardionovum, Bonn, Germany).

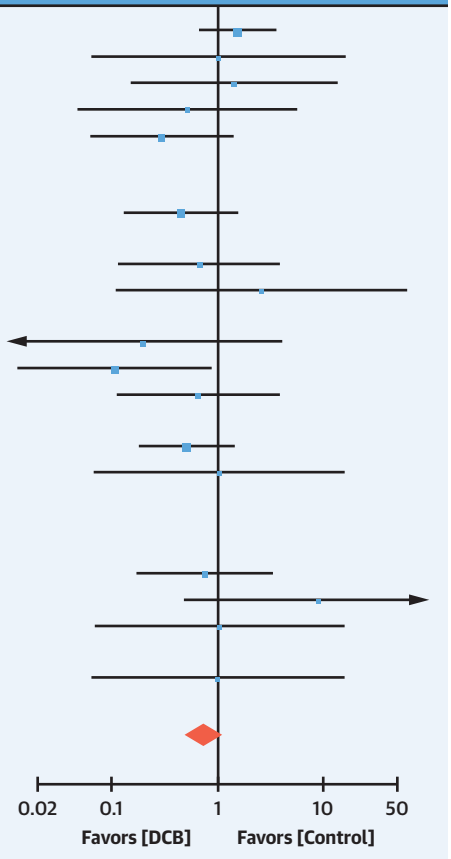
BMS = bare-metal stent; EES = everolimus-eluting stent; FFR = fractional flow reserve; FU = follow-up; HBR = de novo lesions in patients at high bleeding risk; ISR = in-stent restenosis; LLL = late lumen loss; MACE = major adverse cardiac events; MLD = minimal lumen diameter at follow-up angiography, diameter stenosis at follow-up angiography; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; PES = paclitaxel-eluting stent; POBA = plain old balloon angioplasty; SB BIF = side branch bifurcation lesion; SES = sirolimus-eluting stents; STEMI = ST-segment elevation myocardial infarction; SVD = small vessel disease; TLF = target lesion failure; TLR = target lesion revascularization; ZES = zotarolimus-eluting stent.

treated with DCB versus non-DCB devices. The assessment of the primary outcome was based on an intention-to-treat analysis. The number of patients lost to follow-up was observed at different time points. The primary outcome was assessed at different time points according to the available data (6 to 12 months, 2 years, and at least 3 years of follow-up). The differences in mortality rates across the groups were determined and presented using Forest plot as risk ratios (RRs) with corresponding 95% confidence intervals (CIs) for each trial. We used RR as a measure of relative risk. The data from each trial were pooled using fixed (Mantel-Haenszel, Rothman-Boice) or random-effects (DerSimonian-Laird) models, as appropriate. Statistical heterogeneity between the trials was assessed using Cochran's Q test and I^2 statistic. Relevant statistical heterogeneity was considered as Cochran's Q test $p < 0.05$ and $I^2 > 50\%$. The fixed effects model was applied for estimation of RR for the main outcomes (all-cause and cardiac mortality), when the 2 heterogeneity criteria did not appear to be met. In addition, the random effects model of all-cause and cardiac mortality for the whole patient population are visualized in the Online Appendix. Furthermore, for the purpose of the subgroup analysis, we used the random-effects model to account for a low event rate across different subgroups. The presence of a potential publication bias for the specific outcome was assessed visually using Funnel plots, only in cases where the data from a minimum of 10 trials entered the analysis. All statistical analyses were conducted by using Review Manager (RevMan) version 5.3 (2014, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). All p values were 2-sided, with $p < 0.05$ considered as significant. The secondary endpoint was cardiac mortality at 6 to 12 months, 2 years, and at least 3 years of follow-up. The methods and results of this meta-analysis were validated by an independent team of statisticians (Y.Y.).

FIGURE 2 All-Cause Mortality Within 1 Year

Study or Subgroup	DCB Events	DCB Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Basket Small 2	14	382	9	376	14.6%	1.53 [0.67, 3.49]
BELLO	1	90	1	92	1.6%	1.02 [0.06, 16.10]
Biolux RCT	3	147	1	70	2.2%	1.43 [0.15, 13.49]
DARE	1	137	2	141	3.2%	0.51 [0.05, 5.61]
DEBUT	2	102	7	106	11.1%	0.30 [0.06, 1.40]
Gobic STEMI	0	38	0	37		Not estimable
Habara 2011	0	25	0	25		Not estimable
ISAR DESIRE III	3	137	13	265	14.3%	0.45 [0.13, 1.54]
Nishiyama 2016	0	27	0	33		Not estimable
Paccocath ISR I/II	2	54	3	54	4.8%	0.67 [0.12, 3.83]
Patent C	1	33	0	28	0.9%	2.56 [0.11, 60.44]
PEPCAD BIF	0	32	0	32		Not estimable
PEPCAD China ISR	0	109	2	106	4.1%	0.19 [0.01, 4.01]
PEPCAD DES	1	72	5	38	10.5%	0.11 [0.01, 0.87]
PEPCAD II	2	66	3	65	4.9%	0.66 [0.11, 3.80]
PEPCAD Japan SVD	0	92	0	41		Not estimable
PEPCAD NSTEMI	5	104	10	106	15.9%	0.51 [0.18, 1.44]
PICCOLETO	1	28	1	29	1.6%	1.04 [0.07, 15.77]
Restore China SVD	0	116	0	114		Not estimable
Restore Korea	0	86	0	86		Not estimable
Revelation	0	60	0	60		Not estimable
RIBS IV	3	154	4	155	6.4%	0.75 [0.17, 3.32]
RIBS V	4	95	0	94	0.8%	8.91 [0.49, 163.15]
SEDUCE	1	24	1	25	1.6%	1.04 [0.07, 15.73]
Shin 2015	0	44	0	22		Not estimable
TIS	1	68	1	68	1.6%	1.00 [0.06, 15.66]
Total (95% CI)		**2,322**		**2,268**	**100.0%**	**0.74 [0.51, 1.08]**
Total events	45		63			

Heterogeneity: $Chi^2 = 13.55$, df = 16 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 1.57 (P = 0.12)



Forest plot as risk ratios (RRs) with corresponding 95% confidence intervals (CIs) for each trial using an M-H fixed effect model. The **size of central markers** reflects the weight of each study. ISR = in-stent restenosis; M-H = Mantel-Haenszel; RCT = randomized controlled trial; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Figure 1.

RESULTS

Initially, our search yielded 3,073 papers. After removing duplicates, 973 papers were further manually reviewed according to the titles and abstracts, excluding another 865 ineligible papers. A total of 108 potentially eligible papers were full-text reviewed, ultimately identifying 26 papers fulfilling the predefined criteria for inclusion. The study selection process is depicted in the flow diagram (Figure 1).

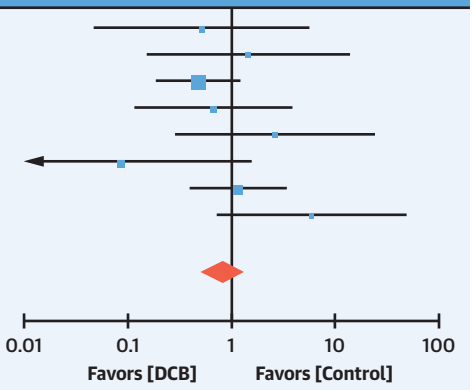
A total of 4,590 patients from 26 RCTs published between 2006 and 2019 were included in the analysis. Of those, 2,322 were randomized to DCBs only and 2,268 patients to alternative treatment. The paclitaxel iopromide-coated DCB SeQuent Please or its successor SeQuent Please Neo (B.Braun, Berlin, Germany) was used most frequently (19 studies) (4,5,10,11,16,18,19,21-39). In addition, the Paccocath ISR study investigated the same paclitaxel iopromide coating (40-42). Pantera Lux (Biotronik, Berlin, Germany) was used in 2 studies (14,43), and the other coatings were used in single studies only (15,17,44-47). Comparator groups were conventional uncoated POBA (6 trials), uncoated scoring balloon angioplasty (1 trial), and BMS or DES (20 trials). The most commonly used stents were everolimus-eluting stents, followed by paclitaxel-eluting stents (PES), sirolimus-eluting stents, and zotarolimus-eluting stents.

Inclusion criteria were lesion-specific, such as treatment of ISR or specific de novo lesions, or defined by the clinical presentation of the patient, such as high bleeding risk or acute coronary

FIGURE 3 All-Cause Mortality Within 2 Years

Study or Subgroup	DCB Events	DCB Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BELLO	1	90	2	92	6.0%	0.51 [0.05, 5.54]
Biolux RCT	3	143	1	69	4.1%	1.45 [0.15, 13.66]
DEBUT	6	102	13	106	38.9%	0.48 [0.19, 1.21]
Paccocath ISR I/II	2	54	3	54	9.2%	0.67 [0.12, 3.83]
Patent C	3	32	1	28	3.3%	2.63 [0.29, 23.82]
PEPCAD China ISR	0	107	5	102	17.2%	0.09 [0.00, 1.55]
RIBS IV	7	154	6	155	18.3%	1.17 [0.40, 3.41]
RIBS V	6	95	1	94	3.1%	5.94 [0.73, 48.37]
Total (95% CI)		**777**		**700**	**100.0%**	**0.84 [0.51, 1.37]**
Total events	28		32			

Heterogeneity: $Chi^2 = 8.99$, df = 7 (P = 0.25); $I^2 = 22\%$
Test for overall effect: Z = 0.71 (P = 0.48)



Forest plot as RRs with corresponding 95% CIs for each trial using an M-H fixed effect model. The **size of central markers** reflects the weight of each study. DCB = drug-coated balloon. Abbreviations as in Figures 1 and 2.

syndrome. The most common indication was treatment of ISR, with 14 studies followed by small coronary vessels with 5 randomized trials (Table 1). The maximum reported clinical follow-up time was up to 12 months in 14 trials, up to 2 years in 3 trials, and at least 3 years in 9 trials.

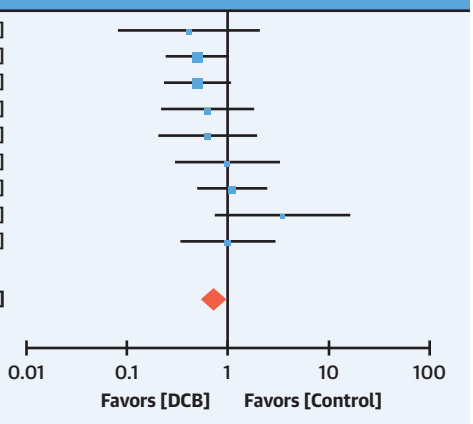
At 6 to 12 months of follow-up (n = 4,590; 26 RCTs), no significant difference in all-cause mortality was seen, however DCB treatment was associated with a numerically lower mortality risk (RR: 0.74; 95% CI: 0.51 to 1.08; p = 0.116) (Figure 2). At 2-year follow-up (n = 1,477; 8 RCTs), the risk of death was similar between the groups (RR: 0.84; 95% CI: 0.51 to 1.37; p = 0.478) (Figure 3). At 3-year follow-up (n = 1,775; 9 RCTs), all-cause mortality was significantly lower in the DCB group when compared with control treatment (RR: 0.73; 95% CI: 0.53 to 1.00; p = 0.047) (Figure 4) with a number needed-to-treat of 36 to prevent 1 death.

Cardiac mortality was also comparable after 1 year (RR: 0.88; 95% CI: 0.55 to 1.40; p = 0.582) (Figure 5)

FIGURE 4 All-Cause Mortality Within 3 Years

Study or Subgroup	DCB Events	DCB Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BELLO	2	90	5	92	5.8%	0.41 [0.08, 2.05]
DEBUT	10	102	21	106	24.2%	0.49 [0.25, 1.00]
ISAR DESIRE III	8	137	31	265	24.8%	0.50 [0.24, 1.06]
Paccocath ISR I/II	5	54	8	54	9.4%	0.63 [0.22, 1.79]
PEPCAD DES	6	72	5	38	7.7%	0.63 [0.21, 1.94]
PEPCAD II	5	66	5	65	5.9%	0.98 [0.30, 3.24]
RIBS IV	12	154	11	155	12.9%	1.10 [0.50, 2.41]
RIBS V	7	95	2	94	2.4%	3.46 [0.74, 16.24]
TIS	6	68	6	68	7.0%	1.00 [0.34, 2.95]
Total (95% CI)		**838**		**937**	**100.0%**	**0.73 [0.53, 1.00]**
Total events	61		94			

Heterogeneity: $Chi^2 = 8.30$, df = 8 (P = 0.40); $I^2 = 4\%$
Test for overall effect: Z = 1.99 (P = 0.05)

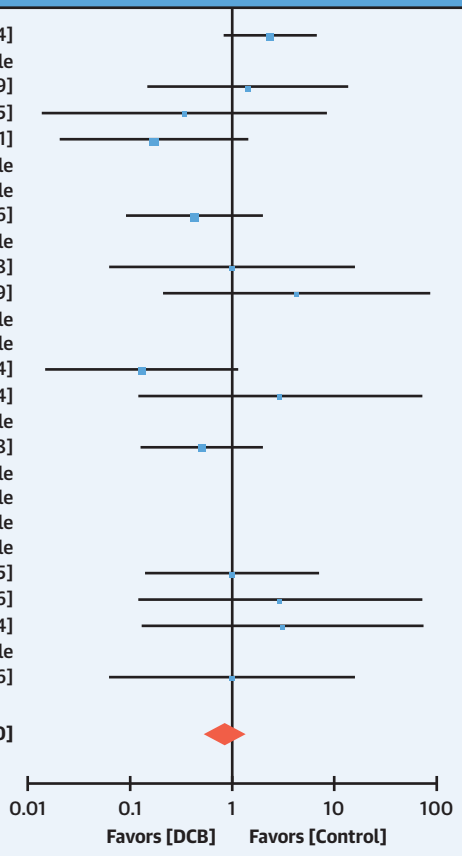


Forest plot as RRs with corresponding 95% CIs for each trial using an M-H fixed effect model. The **size of central markers** reflects the weight of each study. Abbreviations as in Figures 1 and 2.

FIGURE 5 Cardiac Mortality Within 1 Year

Study or Subgroup	DCB Events	DCB Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Basket Small 2	12	382	5	376	13.6%	2.36 [0.84, 6.64]
BELLO	0	90	0	92		Not estimable
Biolux RCT	3	147	1	70	3.7%	1.43 [0.15, 13.49]
DARE	0	137	1	141	4.0%	0.34 [0.01, 8.35]
DEBUT	1	102	6	106	15.9%	0.17 [0.02, 1.41]
Gobic STEMI	0	38	0	37		Not estimable
Habara 2011	0	25	0	25		Not estimable
ISAR DESIRE III	2	137	9	265	16.5%	0.43 [0.09, 1.96]
Nishiyama 2016	0	27	0	33		Not estimable
Paccocath ISR I/II	1	54	1	54	2.7%	1.00 [0.06, 15.58]
Patent C	2	33	0	28	1.5%	4.26 [0.21, 85.29]
PEPCAD BIF	0	32	0	32		Not estimable
PEPCAD China ISR	0	109	0	106		Not estimable
PEPCAD DES	1	72	4	38	14.1%	0.13 [0.02, 1.14]
PEPCAD II	1	66	0	65	1.4%	2.96 [0.12, 71.24]
PEPCAD Japan SVD	0	92	0	41		Not estimable
PEPCAD NSTEMI	3	104	6	106	16.0%	0.51 [0.13, 1.98]
PICCOLETO	0	28	0	29		Not estimable
Restore China SVD	0	116	0	114		Not estimable
Restore Korea	0	86	0	86		Not estimable
Revelation	0	60	0	60		Not estimable
RIBS IV	2	154	2	155	5.4%	1.01 [0.14, 7.05]
RIBS V	1	95	0	94	1.4%	2.97 [0.12, 71.96]
SEDUCE	1	24	0	25	1.3%	3.12 [0.13, 73.04]
Shin 2015	0	44	0	22		Not estimable
TIS	1	68	1	68	2.7%	1.00 [0.06, 15.66]
Total (95% CI)		**2,322**		**2,268**	**100.0%**	**0.88 [0.55, 1.40]**
Total events	31		36			

Heterogeneity: $Chi^2 = 13.61$, df = 13 (P = 0.40); $I^2 = 5\%$
Test for overall effect: Z = 0.55 (P = 0.58)

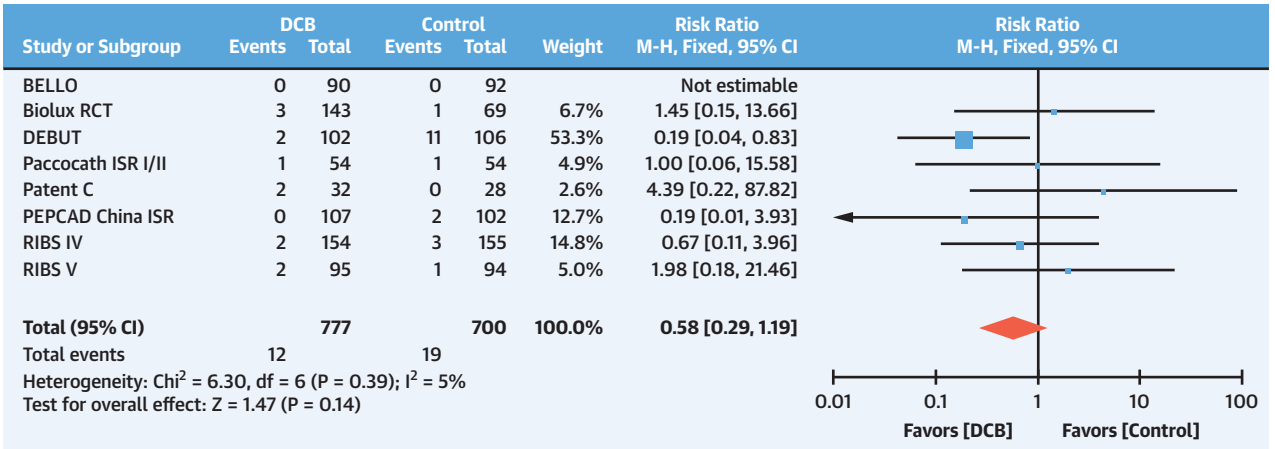


Forest plot as RRs with corresponding 95% CIs for each trial using an M-H fixed effect model. The **size of central markers** reflects the weight of each study. Abbreviations as in Figures 1 and 2.

and 2-year follow-up (RR: 0.58; 95% CI: 0.29 to 1.19; p = 0.140) (Figure 6), respectively. Here, too, a significantly better survival after DCB compared with control subjects was observed after 3 years (RR: 0.53; 95% CI: 0.33 to 0.85; p = 0.009) (Figure 7).

A subgroup analysis of paclitaxel-coated balloons versus uncoated devices (POBA or BMS) showed a significant benefit for paclitaxel-coated devices at 1 year in all-cause mortality (RR: 0.41; 95% CI: 0.21 to 0.80; p = 0.008) and cardiac mortality (RR: 0.43; 95% CI: 0.20 to 0.93; p = 0.033). The mortality benefit at 3 years was mainly driven by trials investigating the treatment of coronary de novo lesions. Target lesion revascularization rates were not different between DCB and alternative treatments at all time points. The incidence of myocardial infarction was significantly lower following DCB treatment at 1 year (RR: 0.60; 95% CI: 0.41 to 0.89; p = 0.01), but not at 2 years (RR: 0.62; 95% CI: 0.37 to 1.03; p = 0.06), and 3 years (RR: 0.80; 95% CI: 0.47 to 1.34; p = 0.39). Furthermore, we performed an analysis excluding studies with PES as active treatment. Similarly, all-cause mortality was not different at 1- and 2-year follow-up. At 3 years, DCB treatment was associated with a numerically lower risk for all-cause mortality; the difference, however, did not reach statistical significance. Cardiac mortality remained significantly lower at 3 years for DCB compared with control treatment without PES. When comparing the DCB exclusively with newer-generation limus-DES, there was no significant difference in all-cause and cardiac mortality observed. Of note, the comparison after 2 and 3 years was based on only 3 studies. Further details on the previously mentioned subgroup analysis are provided in the Online Appendix.

FIGURE 6 Cardiac Mortality Within 2 Years



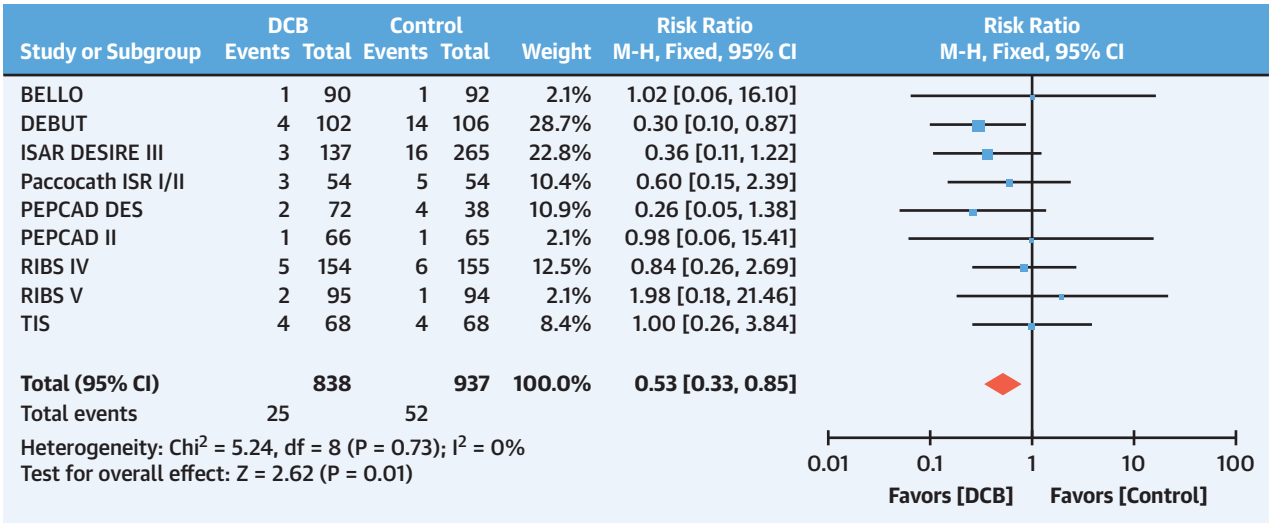
Forest plot as RRs with corresponding 95% CIs for each trial using an M-H fixed effect model. The **size of central markers** reflects the weight of each study. Abbreviations as in Figures 1 and 2.

STUDY QUALITY AND PUBLICATION BIAS. All included studies were considered high-quality trials (with Jadad score of 3), although all trials were open-label trials. There were no signs of publication bias across analyzed studies.

DISCUSSION

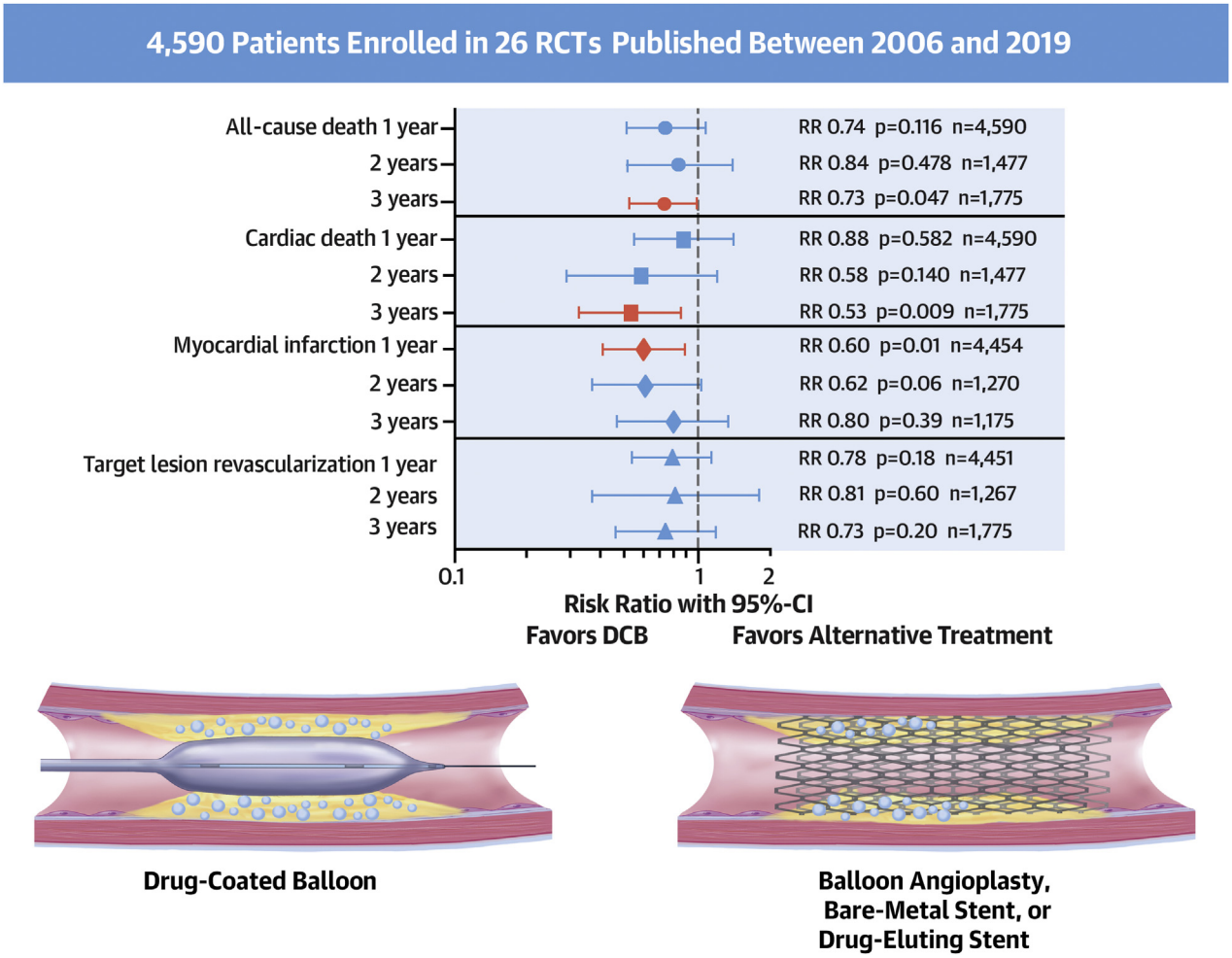
Drug-coated balloons represent accepted, guideline-recommended treatment strategies for ISR (1), and existing evidence suggests that they may also be useful in small vessel disease (4,15) and high-bleeding risk patients (5). Recently however, concerns about the safety of paclitaxel-coated devices in patients with PAD have been expressed (6). In the present meta-analysis, the use of paclitaxel DCB for treatment of CAD was not associated with increased mortality, as was suggested for PAD (Central Illustration). Instead, the risk of death was significantly lower in patients treated with coronary paclitaxel-coated balloons at

FIGURE 7 Cardiac Mortality Within 3 Years



Forest plot as RRs with corresponding 95% CIs for each trial using an M-H fixed effect model. The **size of central markers** reflects the weight of each study. Abbreviations as in Figures 1 and 2.

CENTRAL ILLUSTRATION **Summary of Treatment Effects for Paclitaxel-Coated Balloon Versus Alternative Treatments**



Scheller, B. et al. J Am Coll Cardiol. 2020;75(9):1017-28.

Relative risk of all-cause death **(circles)**, cardiac death **(squares)**, myocardial infarction **(triangles)**, and target lesion revascularization **(diamonds)** at 1, 2, and 3 years post-treatment. **Blue** indicates nonsignificant difference and **red** indicates statistical significant difference.

longer-term follow-up when compared with control subjects, reassuring the safety of these devices when used in coronary arteries.

Local intravascular drug delivery by DES significantly limits restenosis by inhibition of neointimal proliferation. However, neo-atherosclerosis induced by a permanent drug-eluting implant may become a long-term issue after DES implantation (48), which could explain the occurrence of late device-related events (2). Long-term data up to 16 years indeed document an elevated risk for vessel thrombosis and myocardial infarction with BMS or DES when compared with POBA only (49). A nonstent-based method of intramural drug delivery became embodied in the DCB concept using a paclitaxel iopromide balloon coating (50), which was used in the majority of trials included in this meta-analysis (4,5,10,11,16,18,19,21-42). Treatment of ISR with DCB has the advantage of: 1) avoiding multiple layers of metal; 2) reducing the need for prolonged dual antiplatelet therapy; and 3) allowing for repeatability of the procedure. The DAEDALUS patient-level meta-analysis reported in ISR treatment a slightly higher target lesion revascularization rate after DCB with concomitant numerically but not statistically significant difference in favor of paclitaxel-coated balloons

in major clinical safety endpoints such as death and myocardial infarction as compared with DES. However, the trend disappeared when only second-generation DES were studied (51). This finding may be explained by an elevated stent thrombosis risk associated with multiple DES layers (52). The treatment of de novo lesions with DCB still encounters major acceptance issues. The argument against DCB use is usually based on the acute angiographic result with early recoil and concerns about dissections causing acute vascular occlusions. Interestingly, a propensity-matched analysis from the SCAAR registry comprising 2,394 patients found a significant lower rate of target lesion thrombosis after a "DCB only" approach when compared with current-generation DES (adjusted RR: 0.18; 95% CI: 0.04 to 0.82; $p = 0.03$) (53). Of note, in the BASKET SMALL 2 and DEBUT trials there was no acute case of vessel closure in "DCB only" treated patients reported (4,5).

In our meta-analysis, the use of paclitaxel DCB for treatment of CAD was associated with a 27% relative risk reduction in all-cause mortality after 3 years of follow-up with a number needed to treat of 36 to prevent 1 death. One may speculate that this is related to a significant reduction in the number and length of permanent implants, which should lead to a reduction in stent-associated short- and long-term events. Second, and at the same time, appropriate lesion preparation may help identify lesions at risk that require stent treatment. Last, local drug application reduces the restenosis probability comparable to the same order of magnitude as DES (54). Interestingly, a subgroup analysis of our study compared treatment with paclitaxel via DCB versus treatment without local drug administration (POBA or BMS) and revealed a survival advantage for local paclitaxel application already after 1 year. Furthermore, reduced rates of cardiac mortality at 3 years following DCB treatment were also observed when paclitaxel-eluting stents as control treatment were excluded.

In PAD management, DCBs were about to become the standard therapy for the transfemoral region. However, a meta-analysis published in December 2018 reported an increased mortality in the selected trials with ≥2 years follow-up after treatment with paclitaxel-coated stents or balloons (6). Although the meta-analysis derived from peripheral arteries has considerable methodological shortcomings (6) and other more recent data, including patient-level analyses (8) and large case numbers from claims data (9), have not confirmed the safety concerns, use of paclitaxel-coated devices has come under greater scrutiny requiring reasonable assurance of safety. Nevertheless, the criticism on the meta-analysis in PAD (6) includes a selection bias in longer follow-up (e.g., exclusion of trials with numerically lower mortality in the DCB group) and accounting for wrong numbers. The published mortality rates derived from the entire population enrolled at baseline was based on the intention-to-treat principle, which did not consider the influence of cross-over between groups and loss to follow-up. In the past, such an approach has raised doubts about the safety of coronary sirolimus DES (55,56) involving vigilance by regulatory authorities, which were not reproduced by patient-level analyses (57).

The underlying mechanisms of the findings in PAD remain elusive as the low solubility of paclitaxel prevents immediate dissolution following contact with blood, limits loss of paclitaxel from balloon, modulates efficacy and toxicity by limiting the maximum achievable concentration, and contributes to the long-lasting efficacy (58,59). Paclitaxel concentrations in the vessel wall immediately after DCB inflation are far above its solubility representing the sum of dissolved (i.e., the pharmacologically active drug) plus solid crystalline paclitaxel, which serves as a reservoir but does not exhibit toxicity or pharmacological effects (58). Biologically effective cytotoxic tissue levels cannot be reached within the first 24 h (59). The dose administered by a coronary DCB is approximately 750 times lower compared with systemic cancer therapy, challenging the plausibility of a drug effect when local therapies do not have systemic effects. Alternative explanations for the increased mortality observed in PAD patients may include other, nondevice-related issues, such as interactions with health care providers, unmeasured confounders, management of comorbidities, and strategies for secondary prevention (7).

STUDY STRENGTHS AND LIMITATIONS. Our analysis considered patient numbers lost to follow-up at different time points. However, the analysis was conducted at a study level rather than a patient level. We have made every effort to achieve the best possible data quality by involving the principal investigators of most of the included trials. Most of the studies were powered for surrogate angiographic endpoints. The majority of available studies using non-iopromide-coated balloons were small (apart from the iopromide paclitaxel DCB), which limited the possibility of conducting additional analysis comparing different DCB technologies. Furthermore, cross-over treatment could not be assessed systematically, because this information was not provided in most of the publications. Information on concomitant medication, such as antiplatelet and statin therapy, was incompletely available and could therefore not be

investigated. Advances in stent design and evolution of comedication regimens, especially of the ones used in earlier studies, could be associated with improved outcomes and may have influenced the findings.

CONCLUSIONS

The use of paclitaxel DCB for treatment of CAD was associated with lower risk of death at longer-term follow-up when compared with control subjects. These data reassure the safety of these devices, when used in coronary arteries.

ADDRESS FOR CORRESPONDENCE: Prof. Dr. Bruno Scheller, Clinical and Experimental Interventional Cardiology, University of Saarland, Kirrberger Strasse, 66421, Homburg/Saar, Germany. E-mail: bruno.scheller@uks.eu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Meta-analysis of data from randomized trials of coronary intervention found no increase in mortality among patients treated with paclitaxel-coated balloons. In fact, in contrast to reported experience with paclitaxel-coated devices for superficial femoral artery interventions, paclitaxel-coated coronary balloons were associated with a trend toward lower mortality compared with control treatments.

TRANSLATIONAL OUTLOOK: Additional long-term follow-up data are needed to confirm whether a survival advantage associated with DCB-based therapy should change the priority of primary stent deployment in patients undergoing PCIs.

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KEY WORDS drug-coated balloon, paclitaxel, percutaneous coronary intervention

APPENDIX For supplemental figures, please see the online version of this paper.