Individual patient data meta-analysis of paclitaxel-coated balloons vs. drug-eluting stents for small-vessel coronary artery disease: the ANDROMEDA study

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Abstract

Background and Aims	In randomized clinical trials of patients undergoing percutaneous coronary intervention (PCI) for *de novo* small-vessel coronary artery disease (SV-CAD), paclitaxel-coated balloon (PCB) angioplasty showed mid-term angiographic or clinical non-inferiority to drug-eluting stent (DES) implantation. Nevertheless, these trials have sample size limitations, and the relative safety and efficacy beyond the first year remain uncertain.
Methods	The ANDROMEDA study was a collaborative, investigator-initiated, individual patient data meta-analysis comparing 3 year clinical outcomes between PCB angioplasty and DES implantation for the treatment of *de novo* SV-CAD. Multiple electronic databases (PubMed, Scopus, ScienceDirect, and Web of Science) were searched from May 2010 to June 2024 to identify eligible trials. All the following eligibility criteria were required: (i) random allocations of treatments; (ii) patients with SV-CAD; (iii) treatment with PCB or DES; and (iv) clinical follow-up of at least 36 months. The primary and co-primary endpoints were major adverse cardiac events (MACE) and target lesion failure (TLF), respectively. The protocol was registered with PROSPERO (CRD42023479035).
Results	Individual patient data from three randomized trials, including a total of 1154 patients and 1360 lesions, were combined. At 3 years, PCB was associated with a lower risk of MACE compared with DES [hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.47–0.96], due to a lower risk of myocardial infarction and target vessel revascularization. This benefit persisted after multivariable adjustment (HR 0.75, 95% CI 0.58–0.96), but did not reach statistical significance in the two-stage analysis (HR 0.67, 95% CI 0.43–1.04). At the landmark analysis, the risk of MACE between groups was consistent over time. At 3 years, TLF was not significantly different between PCB and DES groups. Reconstructed time-to-event information from a fourth trial was included in a sensitivity analysis (1384 patients and 1590 lesions), showing consistent results in terms of TLF (HR 0.87, 95% CI 0.63–1.20). The comparison between PCB and second-generation DES did not reveal significant differences in 3 year TLF (HR 1.03, 95% CI 0.70–1.50).

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Conclusions   In patients undergoing PCI for *de novo* SV-CAD, PCB angioplasty is associated with a reduction in MACE and a non-significant difference in TLF at 3 year follow-up compared with DES implantation. The restriction of the comparator group to second-generation DES does not alter the main conclusions. Larger trials comparing contemporary devices at a more prolonged follow-up are warranted to confirm these findings.

Structured Graphical Abstract

Key Question

In patients with small vessel coronary artery disease (SV-CAD) amenable to treatment by percutaneous coronary intervention (PCI), does paclitaxel-coated balloon (PCB) angioplasty have similar effectiveness and safety compared with drug-eluting stent (DES) implantation?

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Key Finding

In this individual patient data meta-analysis comparing 3-year clinical outcomes between PCB angioplasty and DES implantation for the treatment of de novo SV-CAD, PCB angioplasty was associated with a lower risk of major adverse cardiac events as compared to DES implantation. Target lesion failure was similar between the two groups.

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Take Home Message

Larger trials comparing contemporary devices at a more prolonged follow-up are warranted to confirm these findings which might impact on daily clinical practice.
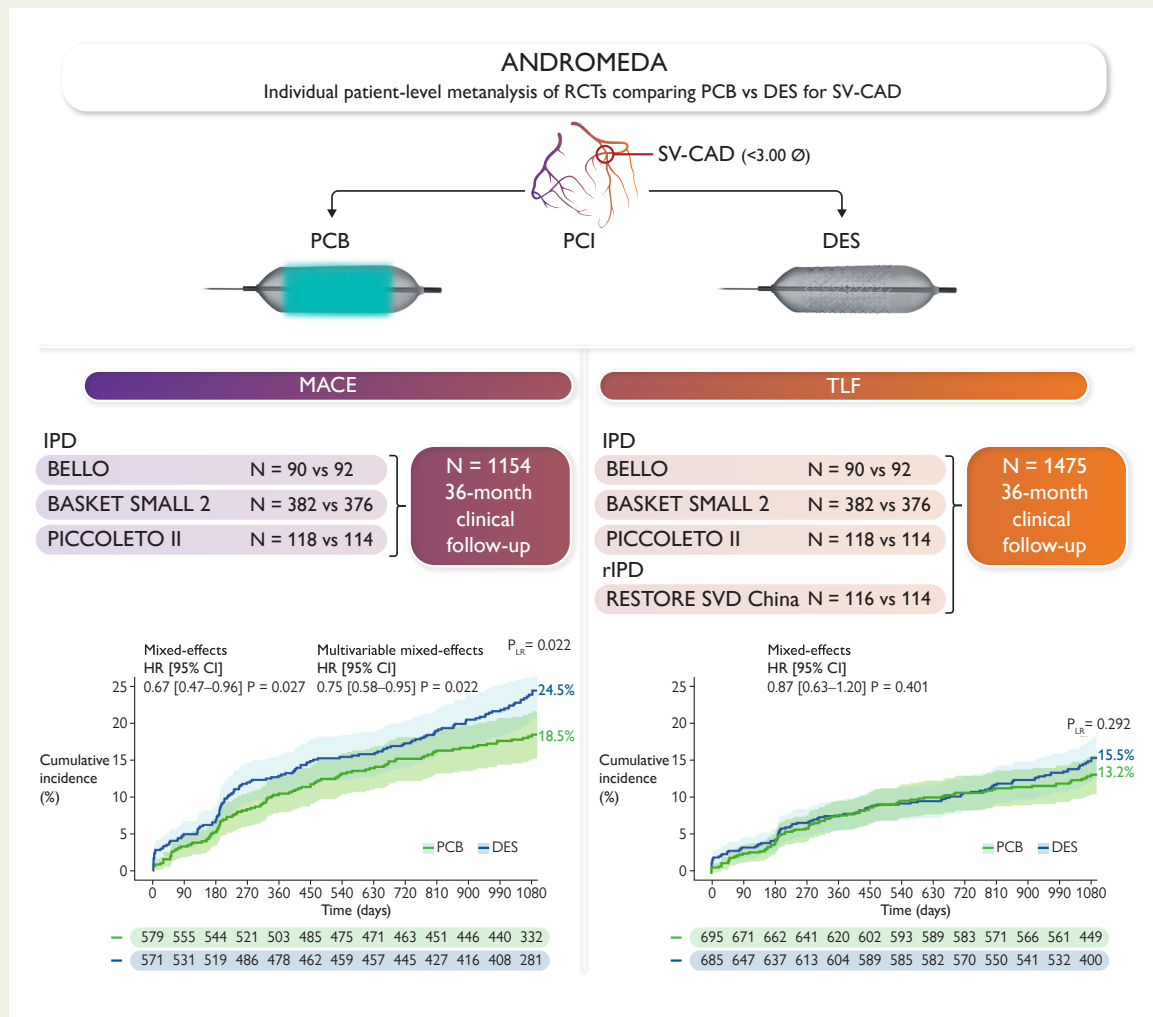
The Assessment of long-term clinical outcomes of *de Novo* DCB peRformance: a cOmprehensive, individual patient data Meta-Analysis of ranDomized clinical triAls (ANDROMEDA) study, an individual patient data meta-analysis of three randomized trials (1154 patients and 1360 lesions), compared 3 year outcomes of PCB angioplasty vs. DES implantation for the treatment of SV-CAD. Patients assigned to PCB showed a

reduced risk of MACE compared with those assigned to DES. After adding reconstructed time-to-event individual patient data from a fourth trial, the analysis of the co-primary outcome of TLF did not show significant differences between treatment groups. CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; IPD, individual patient data; MACE, major adverse cardiac event; P_{LR}, P-value of the log-rank test; PCB, paclitaxel-coated balloon; RCT, randomized clinical trial; rIPD, reconstructed time-to-event individual patient data; SV-CAD, small-vessel coronary artery disease; TLF, target lesion failure.

Introduction

The introduction of stents during percutaneous coronary intervention (PCI) aimed to overcome the occurrence of acute elastic recoil and seal flow–limiting dissections associated with plain balloon angioplasty.[1,2] Drug-eluting stent (DES) implantation has been proven to be both safe and effective in reducing the incidence of device- and vessel-oriented adverse events, granting endorsement by current guidelines.[3,4] However, the use of permanent metallic implants comes with some potential drawbacks, including the requirement for prolonged dual antiplatelet therapy with an inherent increase in haemorrhagic events, particularly in elderly patients and those deemed at high bleeding risk.[5–8] Moreover, a constant risk of long-term stent-related complications (i.e. in-stent restenosis, stent thrombosis, and neoatherosclerosis) with an incidence rate of ~2%–3% per stent per year, persisting beyond the first year, has been described with current-era devices.[9–11]

Drug-coated balloons (DCBs) enable a stent-free approach, which is particularly appealing in the context of small-vessel coronary artery disease (SV-CAD), where PCI with DES is hampered by an inverse relationship between the reference vessel diameter and the risk of developing restenosis,[10,12] and it is estimated an almost two-fold higher risk of target lesion failure (TLF) at 1 year compared with the treatment of non-small vessels.[13,14] In the setting of SV-CAD, paclitaxel-coated balloon (PCB) angioplasty has been associated with similar clinical outcomes compared with DES implantation.[15–18] However, most of the available trials had insufficient power to assess clinical outcomes, and information about the long-term safety and efficacy of PCB for SV-CAD remains limited. Of note, in some studies, treatment with PCB was associated with a flattening of adverse events after 12 months, possibly related to the absence of permanent metallic implants and the positive remodelling process promoted by paclitaxel.[19,20]

Against this background, we conducted a comprehensive, collaborative meta-analysis of individual patient data from all available randomized clinical trials comparing PCB angioplasty with DES implantation in the setting of de novo SV-CAD with a clinical follow-up time of at least 36 months.

Methods

Study design and search strategy

The Assessment of long-term clinical outcomes of de Novo DCB peRformance: a cOmprehensive, individual patient data Meta-Analysis of ranDomized clinical triAls (ANDROMEDA) was an investigator-initiated, collaborative individual patient data meta-analysis of randomized clinical trials. ANDROMEDA was reported in keeping with the Preferred Reporting Items for Systematic reviews and Meta-Analyses of Individual Patient Data (PRISMA-IPD) recommendations, and the protocol was registered with PROSPERO (CRD42023479035).[21] The study was not supported by extramural funding, and no device manufacturer or company with potential conflicts of interest was involved at any stage.

Multiple electronic databases (PubMed, Scopus, ScienceDirect, and Web of Science) and archives of major scientific societies and international conferences in the field were searched from May 2010 (the first randomized clinical trial on PCB angioplasty for de novo SV-CAD) to June 2024. Trials were deemed eligible for inclusion when all the following criteria were satisfied: (i) random allocations of treatments; (ii) patients with SV-CAD; (iii) treatment with PCB or DES; and (iv) clinical follow-up of at least 36 months. In light of the known heterogeneity in the definition of SV-CAD, an upper reference vessel diameter cut-off of 3.00 mm was used to identify trials on the topic. Trials testing protocol-driven interventional strategies combining DCB angioplasty and DES implantation with other devices were not eligible for inclusion. Except for SV-CAD, restrictions in terms of demographic, biometric, clinical, and angiographic conditions were not imposed. More details on the search strategy are reported in Supplementary data online. After excluding duplicates and merging the records, two investigators (S.F. and D.G.) screened the title and abstract of each report. The remaining potentially includable reports were screened by the same investigators (S.F. and D.G.) at the full-text level. Reports regarding different analyses of the same trial were combined.

The primary investigator of each eligible trial was invited to contribute to the ANDROMEDA study. Data extraction was conducted by the primary investigator of each trial. The variables of interest were selected at the study protocol stage based on clinical relevance and consistency with the original publications. Nevertheless, additional unpublished data, including baseline and procedural characteristics, clinical outcomes, and follow-up variations, were provided when available in the original databases. Before generating the pooled database, the variables of interest were validated by interactive cross-talk between the co-ordinating and collaborating centres. The final database was then generated and stored at the co-ordinating centre. Data supporting study findings are available from the corresponding author upon reasonable request.

The local institutional review boards approved all included trials at each participating centre, and all patients provided written informed consent before randomization. Clinical events and angiographic measurements in each trial were assessed by independent clinical events committees and core laboratories, respectively. The device manufacturers and medical companies with conflicts of interest had no involvement in any stage of the ANDROMEDA study, including decisions regarding data disclosure.

Before performing the statistical analysis, potential sources of bias were assessed by the Risk of Bias 2 tool.[22] After completing the statistical analysis, the overall reliability of conclusions was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[23]

Endpoints

The primary endpoint was a composite of major adverse cardiac events (MACE) including all-cause mortality, myocardial infarction, target lesion thrombosis, or target vessel revascularization. The co-primary endpoint was TLF, a composite of cardiac death, myocardial infarction, or target lesion revascularization. The secondary endpoints included all-cause death, cardiac death, myocardial infarction, target lesion thrombosis, target lesion

revascularization, and target vessel revascularization. The outcomes were assessed at a 3 year follow-up.

Death could be considered cardiac or non-cardiac depending on the cause; if the cause could not be clearly defined, the event was considered as cardiac.[24] Myocardial infarction was defined according to the guidelines at the time of the study, it was determined based on clinical symptoms, the electrocardiogram, and cardiac biomarkers.[24] The Academic Research Consortium criteria for definite or probable stent thrombosis were used to define target lesion thrombosis.[24] Target lesion revascularization, percutaneous or surgical, included any repeat revascularization at the target lesion level.[24]

Statistical analysis

Categorical variables were reported as counts and percentages and compared by Pearson χ^2 test or Fisher's exact test, as appropriate. Continuous variables were summarized as means and standard deviations or medians and interquartile ranges, depending on their distribution, and compared by the Welch t-test or the Mann–Whitney–Wilcoxon U test, respectively. Outcomes were assessed as time-to-first events, primarily according to the intention-to-treat principle and secondarily to the per-protocol principle. In the primary analysis, the outcomes were estimated by one-stage mixed-effects Cox proportional hazards regression models, with treatment assignment as the fixed component and the random component with a random intercept allowing for a different baseline risk across trials and a random slope allowing treatment effect to vary across trials.[25,26] The results were provided by hazard ratios (HRs) with 95% confidence interval (CI) and Wald-type test P-values. The proportional hazards assumption was tested by the Grambsch–Therneau test and Schoenfeld scaled residuals.[26] Cumulative incidences calculated by the Kaplan–Meier method and comparisons of curves by the log-rank test complemented the primary analysis results.

In a sensitivity analysis, after generation of five databases by joint multiple imputation accounting for the multi-level structure of data, multivariable adjustment was performed by including age, gender, body mass index, diabetes, hypertension, hypercholesterolaemia, current smoking status, prior PCI, prior coronary artery bypass grafting, peripheral artery disease, left ventricular ejection fraction, clinical presentation, multivessel disease, bifurcation, device diameter, device length, and DES generation.[27] The results across imputed databases were pooled by Rubin's rules.[27] In another sensitivity analysis, variations over time in the primary and co-primary endpoints were assessed by applying the landmark time point of 12 months. An additional sensitivity analysis was performed by using mixed-effects models with a stratified fixed intercept for the trial of origin and a random slope for the treatment effect across trials.

One-stage analyses were systematically replicated by two-stage sensitivity analyses, in which individual trial estimates were computed by Cox proportional hazards regression and subsequently pooled using random-effects models.[28] Rare outcomes with monotonic distribution within individual trials were computed by Firth's correction.[29] Summary estimates and trial-related effects, along with the corresponding weights based on the inverse of variance, were illustrated by forest plots.[28] Between-trials heterogeneity computed by the restricted maximum likelihood estimator was assessed by τ^2 and I^2 statistics and formally tested.[28]

Planned subgroup analyses for the primary safety and efficacy endpoints using the mixed-effects Cox model included subsets based on the median age (≤ or >67 years), gender, diabetes, acute or chronic coronary syndrome, estimated glomerular filtration rate <60 or ≥60 mL/min/1.73 m^2, device diameter <2.50 or ≥2.50 mm, device length <20 or ≥20 mm, and DES generation. In the latter subgroup analysis, the DCB counterpart was included according to the DES generation used in the trial, and for Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug-Eluting Stents in Small Vessel Interventions (BASKET-SMALL 2), the specific period in which the type of DES was used. Interaction P-values were derived from one-stage mixed-effects models to properly account for the interaction between treatment effect and patient-level covariates.[30]

In the case of significant interaction, P-values were conservatively adjusted for multiplicity by the Benjamini–Hochberg method.[31]

Finally, the unavailability of the Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease (RESTORE SVD China) trial was partially overcome by reconstructing individual patient time-to-event data for TLF from the digitized original Kaplan–Meier curves.[32] The spatial co-ordinates, along with the number of events and numbers at risk between groups, were used to calculate the information of interest.[32] Reconstructed data were combined by both one- and two-stage models to provide a comprehensive analysis including all available clinical trials on the topic.

Results

Details regarding the results of the search and screening of eligible trials are shown in Supplementary data online (see Supplementary data online, *Tables S1* and *S2*, and *Figure S1*). The search process identified four prospective, randomized clinical trials eligible for inclusion in the ANDROMEDA study.[15–19,33–35] The primary investigators of the Balloon Elution and Late Loss Optimization (BELLO), BASKET-SMALL 2, and Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment (PICCOLETO II) adhered to the collaborative study and provided individual patient data.[15,16,18,19,33,34] The primary investigator of the remaining trial (RESTORE SVD China) did not share individual patient data due to time restrictions on data transfer. Nevertheless, individual patient time-to-event data from the RESTORE SVD China trial[35] for the outcome of TLF were reconstructed and pooled data by one- and two-stage analyses to provide a comprehensive analysis of the available evidence. The design and main characteristics of each trial and an overview of the study database completeness are reported in *Table 1* and Supplementary data online, *Tables S3* and *S4*. No relevant issues were identified when assessing individual patient data integrity.

A total of 1154 patients (1360 lesions) randomly assigned to PCB angioplasty (582 patients and 663 lesions) or DES implantation (572 patients and 697 lesions) were combined. The baseline clinical characteristics were generally balanced between groups, except for the younger age at the time of PCI of patients assigned to PCB compared with those assigned to DES (*Table 2*). Although angiographic differences were not significant, some procedural differences were noted (*Table 3*). In more detail, in the DCB group, predilatation was performed more frequently (98.9% vs. 93.4%; $P < .001$) and selecting larger balloons [2.5 (2.0–2.5) vs. 2.2 (2.0–2.5) mm; $P = .030$] than in the DES group. Moreover, DCBs were longer [20.0 (15.0–26.0) vs. 18.0 (15.0–23.0) mm; $P < .001$] and inflated at a lower pressure [10.0 (8.0–14.0) vs. 14.0 (12.0–14.0) atm; $P < .001$] and for a longer time (50.0 (30.0–60.0) vs. 20.0 (10.0–30.0) s; $P < .001$) compared with DES.

Primary and co-primary endpoints

At 3 year follow-up, MACE occurred in 103 patients assigned to PCB angioplasty and 132 assigned to DES angioplasty resulting in a significant difference by one-stage analysis (18.5% vs. 24.5%; HR 0.67, 95% CI 0.47–0.96, $P = .027$; *Table 4*; *Figure 1*). The difference remained consistent after multivariable adjustment (HR 0.75, 95% CI 0.58–0.96, $P = .022$; *Table 4*; *Figure 1*). No significant heterogeneity between 0–1 and 1–3 years was observed ($P_{int} = .692$; *Table 4*; *Figure 1*). The two-stage analysis showed differences in MACE between the PCB and DES groups that did not reach the threshold of statistical significance (HR 0.67, 95% CI 0.43–1.04; $P = .074$; *Table 5*; *Figure 1*). The contribution to the summary estimate of the individual trials was overall

Table 1 Main characteristics of an available randomized clinical trial comparing PCB vs. DES for de novo SV-CAD

Trial	Design	PCB	DES	Bail-out stenting	SV-CAD definition	Primary endpoint	Data availability
BELLO	Randomized (1:1) Open label Core lab CEC	n = 90 Drug: paclitaxel Excipient: urea	n = 92 Drug: paclitaxel Polymer: durable Alloy: stainless steel (97 μm)	20%	RVD <2.80 mm	6 month in-segment LLL (non-inferiority)	Individual patient data
BASKET-SMALL 2	Randomized (1:1) Open label Core lab CEC	n = 382 Drug: paclitaxel Excipient: iopromide	n = 376 (28%/72%) Drug: paclitaxel/everolimus Polymer: durable/durable Alloy: stainless steel (97 μm)/ cobalt-chromium (81 μm)	5%	RVD 2.00– 3.00 mm	12 month MACE (non-inferiority)	Individual patient data
PICCOLETO II	Randomized (1:1) Open label Core lab CEC	n = 118 Drug: paclitaxel Excipient: dextran	n = 114 Drug: everolimus Polymer: durable Alloy: cobalt-chromium (81 μm)	6.7%	RVD 2.00– 2.75 mm	6 month in-segment LLL (non-inferiority)	Individual patient data

Individual patient data from the BELLO, BASKET-SMALL 2, and PICCOLETO II trials were available. The RESTORE SVD China was added for the co-primary endpoint of TLF after reconstructing time-to-event individual patient data.
ACS, acute coronary syndrome; CEC, clinical events committee; DS%, percentage diameter stenosis; LLL, late lumen loss; RVD, reference vessel diameter.

Table 2 Patient-level clinical characteristics

	Total (n = 1154)	PCB (n = 582)	DES (n = 572)	P
Age (years)	67.0 (60.0–75.0)	66.0 (59.0–74.0)	68.0 (60.8–75.0)	.021
Female	278 (24.2)	126 (21.8)	152 (26.6)	.055
Body mass index (kg/m^2)	27.6 (25.0–30.5)	27.8 (25.2–30.8)	27.4 (24.8–30.3)	.079
Diabetes	412 (35.9)	207 (35.8)	205 (36.1)	.904
Oral therapy alone	258 (22.5)	122 (21.1)	136 (23.9)	
Insulin	154 (13.4)	85 (14.7)	69 (12.1)	
Hypertension	960 (83.6)	477 (82.2)	483 (84.9)	.227
Dyslipidaemia	803 (70.2)	407 (70.3)	396 (70.1)	.940
Current smoking	225 (19.9)	123 (21.5)	102 (18.1)	.153
Family history of CAD	362 (33.5)	195 (35.5)	167 (31.4)	.151
Prior PCI	684 (61.6)	346 (61.3)	338 (61.8)	.879
Prior coronary artery bypass grafting	100 (9.0)	50 (8.9)	50 (9.1)	.887
Peripheral artery disease	108 (9.7)	52 (9.2)	56 (10.2)	.567
Left ventricular ejection fraction				.061
Normal	764 (82.7)	377 (80.0)	387 (85.4)	
Mild-moderate reduction	147 (15.9)	88 (18.7)	59 (13.0)	
Severe reduction	13 (1.4)	6 (1.3)	7 (1.5)	
Moderate-severe chronic kidney disease	172 (15.5)	81 (14.5)	91 (16.6)	.331
eGFR (mL/min/1.73 m^2)	84.9 (69.1–96.6)	85.5 (69.3–97.5)	83.9 (68.8–96.0)	.192
Clinical presentation				.290
Silent ischaemia-stable angina	817 (71.2)	407 (70.3)	410 (72.1)	
Unstable angina	161 (14.0)	85 (14.7)	76 (13.4)	
NSTEMI	155 (13.5)	76 (13.1)	79 (13.9)	
STEMI	15 (1.3)	11 (1.9)	4 (0.7)	
Multivessel CAD	872 (76.6)	452 (78.7)	420 (74.5)	.088

The variables are medians (interquartile ranges) or counts (proportions). The information is reported at the patient level.
eGFR, estimated glomerular filtration rate; *NSTEMI*, non–ST-segment elevation myocardial infarction; *STEMI*, ST-segment elevation myocardial infarction.

reasonably balanced, though the BASKET-SMALL 2 weight was higher than that of the other trials (43.8%; *Figure 1*). Moderate-to-high between-trial heterogeneity was detected ($\tau^2 = 0.085$; $I^2 = 57.5\%$; $P = .095$; *Figure 1*). The one-stage (HR 0.64, 95% CI 0.41–0.99, $P = .047$) and two-stage per-protocol analyses were consistent with the primary analyses (see Supplementary data online, *Tables S5* and *S6*).

At 3 year follow-up, TLF occurred in 81 patients assigned to PCB angioplasty, and 93 assigned to DES angioplasty resulting in a non-significant difference by one-stage analysis (14.7% vs. 17.6%; HR 0.78, 95% CI 0.55–1.12, $P = .185$; *Table 4*; *Figure 2*). This result remained consistent after multivariable adjustment (HR 0.86, 95% CI 0.64–1.15, $P = .304$) and no significant heterogeneity between the periods from 0 to 1 year and 1 to 3 years was observed ($P_{int} = .667$; *Table 4*; *Figure 2*). The two-stage analysis did not show significant differences in TLF between the PCB and DES groups (HR 0.77, 95% CI 0.49–

1.21; *Table 5*; *Figure 2*). The contribution to the summary estimate of the individual trials was overall reasonably balanced, though the BASKET-SMALL 2 weight was higher than that of the other trials (48.1%; *Figure 2*). Moderate between-trial heterogeneity was detected ($\tau^2 = 0.071$; $I^2 = 43.9\%$; $P = .168$; *Figure 2*). The one-stage (HR 0.70, 95% CI 0.41–1.19, $P = .190$) and two-stage per-protocol analyses were consistent with the primary analyses (see Supplementary data online, *Tables S5* and *S6*).

The pre-specified analysis of major clinical and angiographic subgroups for MACE and TLF revealed a significant interaction between treatment effects and median age ($P_{int} = .037$ and $P_{int} = .036$, respectively; *Figure 3*). Specifically, the benefit of PCB was driven by the subgroup of patients younger than 67 years (MACE: HR 0.55, 95% CI 0.38–0.81, $P = .002$; TLF: HR 0.62, 95% CI 0.40–0.96, $P = .031$; *Figure 3*). Yet, after adjusting for repeated statistical testing, the

Table 3 Lesion-level angiographic and procedural characteristics

	Total (n = 1360)	PCB (n = 663)	DES (n = 697)	P
Target vessel				.152
Left main	1 (0.1)	0 (0)	1 (0.2)	
Left anterior descending	389 (33.9)	204 (36.6)	185 (31.3)	
Left circumflex	508 (44.3)	240 (43.1)	268 (45.3)	
Right coronary artery	250 (21.8)	113 (20.3)	137 (23.2)	
Bifurcation	29 (2.2)	15 (2.3)	14 (2.1)	.750
Predilatation	1246 (96.1)	620 (98.9)	626 (93.4)	<.001
Maximum predilatation balloon diameter (mm)	2.2 (2.0–2.5)	2.5 (2.0–2.5)	2.2 (2.0–2.5)	.030
Device diameter (mm)	2.5 (2.2–2.5)	2.5 (2.2–2.5)	2.5 (2.2–2.5)	.403
Device diameter groups				.094
≤2.25 mm	375 (27.9)	171 (26.2)	204 (29.6)	
2.50 mm	725 (54.0)	366 (56.0)	359 (52.1)	
2.75 mm	200 (14.9)	90 (13.8)	110 (16.0)	
≥3.00 mm	42 (3.1)	26 (4.0)	16 (2.3)	
Device length (mm)	20.0 (15.0–23.0)	20.0 (15.0–26.0)	18.0 (15.0–23.0)	<.001
Device length ≥20 mm	702 (52.3)	448 (68.7)	254 (36.9)	<.001
Device inflation (atm)	12.0 (10.0–14.0)	10.0 (8.0–14.0)	14.0 (12.0–14.0)	<.001
Inflation time (s)	30.0 (20.0–60.0)	50.0 (30.0–60.0)	20.0 (10.0–30.0)	<.001

The variables are medians (interquartile ranges) or counts (proportions). The information is reported at the lesion level.

Table 4 Outcomes at 3 year follow-up—intention-to-treat one-stage analysis

Outcomes	PCB (n = 582)		DES (n = 572)		P_LR	Mixed-effects model		Multivariable mixed-effects model	
	Events	%	Events	%		HR (95% CI)	P	HR (95% CI)	P
MACE	103	18.5	132	24.5	.022	0.67 (0.47–0.96)	.027	0.75 (0.58–0.96)	.022
TLF	81	14.7	93	17.6	.239	0.78 (0.55–1.12)	.185	0.86 (0.64–1.15)	.304
Death	35	6.3	36	6.7	.851	0.90 (0.56–1.47)	.682	0.98 (0.62–1.55)	.934
Cardiac death	21	3.8	14	2.7	.261	1.78 (0.82–3.88)	.144	1.91 (0.94–3.90)	.075
Myocardial infarction	25	4.7	42	7.8	.026	0.58 (0.35–0.94)	.029	0.52 (0.31–0.85)	.009
Target lesion thrombosis	2	0.4	9	1.7	.032	0.22 (0.05–1.00)	.051	0.20 (0.04–0.96)	.044
Target lesion revascularization	41	7.6	52	10.1	.203	0.73 (0.47–1.13)	.163	0.84 (0.57–1.24)	.382
Target vessel revascularization	60	11.1	82	15.6	.038	0.66 (0.45–0.97)	.035	0.65 (0.45–0.93)	.020

Major adverse cardiac event includes all-cause death, myocardial infarction, or target vessel revascularization. Target lesion failure includes cardiac death, myocardial infarction, or target lesion revascularization.
MACE, major adverse cardiac events; TLF, target lesion failure; P_{LR}, log-rank test P-value.

interaction P-value in both subgroup analyses was no longer significant (0.296 and 0.288, respectively).

Beyond the conclusions in terms of treatments, multivariable analyses for MACE and TLF at 3 year follow-up showed that diabetes and multivessel disease were significant independent predictors (see Supplementary data online, Tables S7 and S8). In the analysis for MACE, current smoking status, admission for non–ST-segment elevation myocardial infarction, and device length showed significant
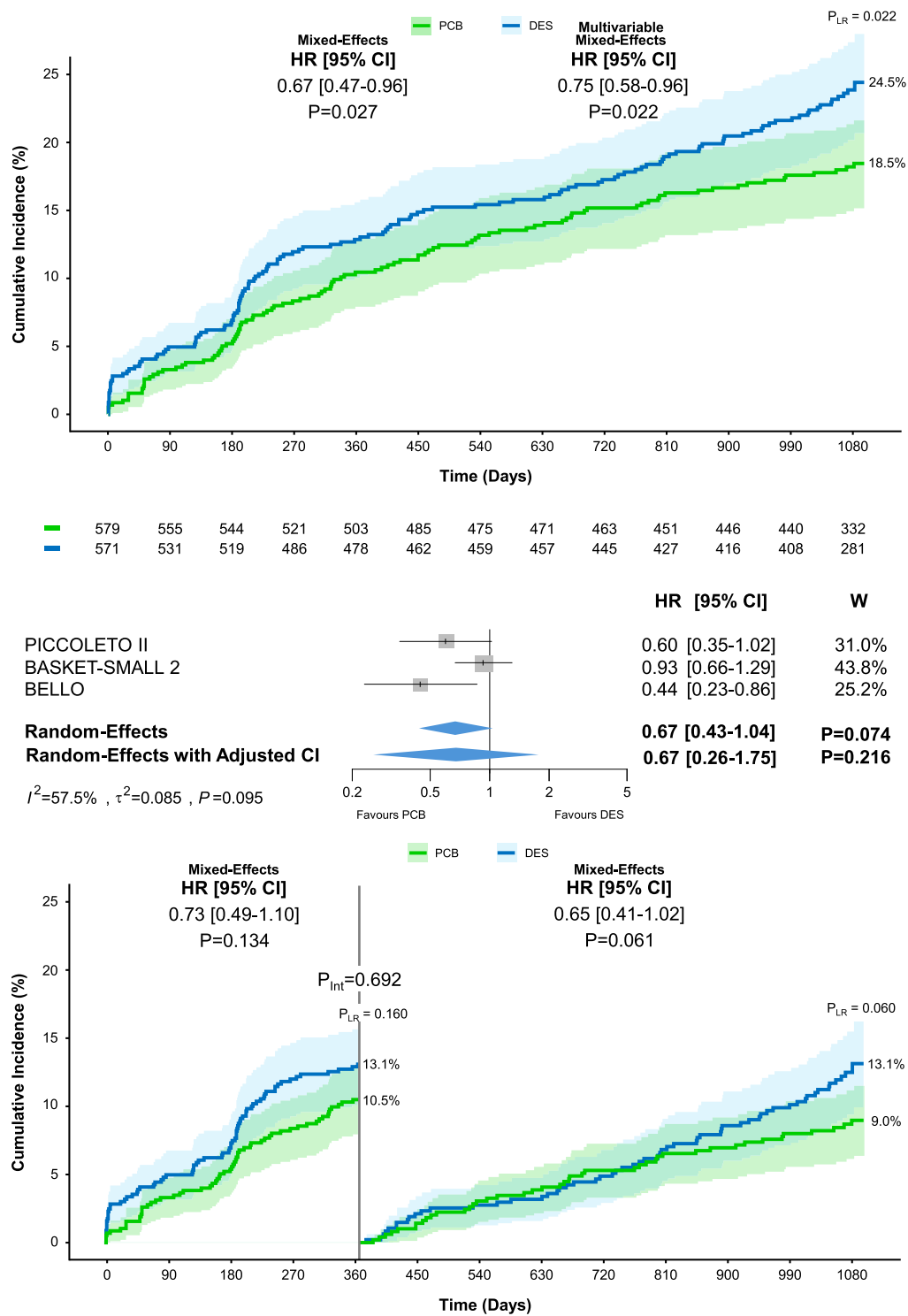
Figure 1 Major adverse cardiac events at 3 year follow-up. Cumulative incidence of major adverse cardiac events including all-cause death, myocardial infarction, and/or target vessel revascularization, in patients allocated to paclitaxel-coated balloon vs. drug-eluting stent. The upper panel shows the results of the one-stage analysis on top and the two-stage analysis below. The lower panel displays the landmark analysis performed at 12 months. The numbers of patients at risk between the treatment groups across the time intervals are shown below the graph. P_{int}, *P*-value of the test for interaction; P_{LR}, *P*-value of the log-rank test; W, weight

Table 5 Outcomes at 3 year follow-up—intention-to-treat two-stage analysis

Outcomes	Random-effects		Heterogeneity		
	HR (95% CI)	P	I^2	τ^2	P_Q
MACE	0.67 (0.43–1.04)	.074	57.5	0.085	.095
TLF	0.77 (0.49–1.21)	.258	43.9	0.071	.168
Death	0.96 (0.60–1.54)	.880	0	0	.557
Cardiac death	1.40 (0.71–2.77)	.328	0	0	.764
Myocardial infarction	0.51 (0.24–1.08)	.078	35.2	0.187	.214
Target lesion thrombosis	0.28 (0.06–1.18)	.082	0	0	.639
Target lesion revascularization	0.77 (0.51–1.17)	.220	0	0	.518
Target vessel revascularization	0.70 (0.48–1.01)	.054	4.3	0.015	.352

Major adverse cardiac event includes all-cause death, myocardial infarction, or target vessel revascularization. Target lesion failure includes cardiac death, myocardial infarction, or target lesion revascularization.
MACE, major adverse cardiac events; TLF, target lesion failure; P_{LR}, log-rank test P-value; P_Q, P-value of the heterogeneity test.

associations (see Supplementary data online, Table S7). The one-stage analysis with alternative modelling (stratified fixed intercept and random slope) showed consistent results (see Supplementary data online, Table S9).

Secondary endpoints

At 3 year follow-up, all-cause and cardiac death were not significantly different between groups across analyses (Tables 4 and 5; see Supplementary data online, Tables S5 and S6). By one-stage analysis, significant reductions in myocardial infarction (4.7% vs. 7.8%; HR 0.58, 95% CI 0.35–0.94, P = .029; HR 0.52, 95% CI 0.31–0.85, P = .009) and target vessel revascularization (11.1% vs. 15.6%; HR 0.66, 95% CI 0.45–0.97, P = .035; HR 0.65, 95% CI 0.45–0.93, P = .020) were observed (Table 4; Figure 1). By two-stage and per-protocol analyses, the differences in myocardial infarction and target vessel revascularization did not reach the threshold of statistical significance (Table 5; see Supplementary data online, Tables S5 and S6). Target lesion thrombosis was significantly reduced in the PCB group compared with the DES group at the one-stage multivariable analysis (HR 0.20, 95% CI 0.04–0.96, P = .044) and per-protocol analyses. The difference did not reach the threshold of statistical significance in the other analyses (Tables 4 and 5; see Supplementary data online, Tables S5 and S6). Target lesion revascularization did not significantly differ between treatment groups across analyses.

Comprehensive assessment of the available evidence and impact of drug-eluting stent generation

After including RESTORE SVD China reconstructed time-to-event individual patient data for the endpoint of TLF, a total of 1384 patients (1590 lesions) were included (Table 1). At 3 years, no significant difference in TLF was detected between PCB and DES groups, regardless of the model employed (13.2% vs. 15.5%; one stage: HR 0.87, 95% CI 0.63–1.20, P = .401; two stage: HR 0.85, 95% CI 0.60–1.19, P = .347; two stage with adjusted CI: HR 0.85, 95% CI 0.48–1.51, P = .432) (Figure 4).

The assessment of the influence of device generation in the DES arm showed a significant reduction of TLF with second-generation DES compared with first-generation DES, and the result remained

consistent after accounting for repeated statistical testing (13.3% vs. 20.1%; HR 0.59, 95% CI 0.36–0.95, P_{adj} = .043). Nevertheless, the comparison between DCB and second-generation did not reveal significant differences (13.0% vs. 13.3%; HR 1.03, 95% CI 0.70–1.50, P = .898; see Supplementary data online, Figure S2).

Assessment of bias and reliably of results

The qualitative assessment of trials did not reveal serious concerns, though the impossibility of masking the assignment to PCB and DES due to intrinsic differences between devices implied a possible source of bias (see Supplementary data online, Figure S3).

The assessment of the available evidence by the GRADE system showed a moderate or high overall quality, depending on the outcome of interest (see Supplementary data online, Table S10).

Discussion

The main analysis of the ANDROMEDA study shows that 3 years following PCI for SV-CAD, patients treated with PCB experience a significantly lower incidence of MACE compared with those treated with DES (Structured Graphical Abstract). This result was mainly driven by lower incidences of myocardial infarction and target vessel revascularization. The 3-year incidence of TLF between treatment groups was not significantly different (Structured Graphical Abstract). Notably, the landmark analysis suggested consistent effects between PCB and DES over time and sensitivity analyses did not reveal significant differences in MACE and TLF between PCB and second-generation DES.

Traditionally, SV-CAD is regarded as a challenging PCI setting due to the established inverse relationship between target vessel segment diameter and restenosis at follow-up.[10,12] Despite substantial advances in stent technologies and procedural optimization, patients undergoing PCI with second-generation DES for SV-CAD continue to exhibit a 1 year risk of TLF almost two-fold higher than those treated for lesions in coronary artery segments with larger diameter.[13,14,36] Against this background, the ANDROMEDA study strengthens previous evidence on SV-CAD by showing in the primary analysis a relative risk reduction in 3-year MACE of up to 33% in patients treated with PCB compared with those treated with DES.
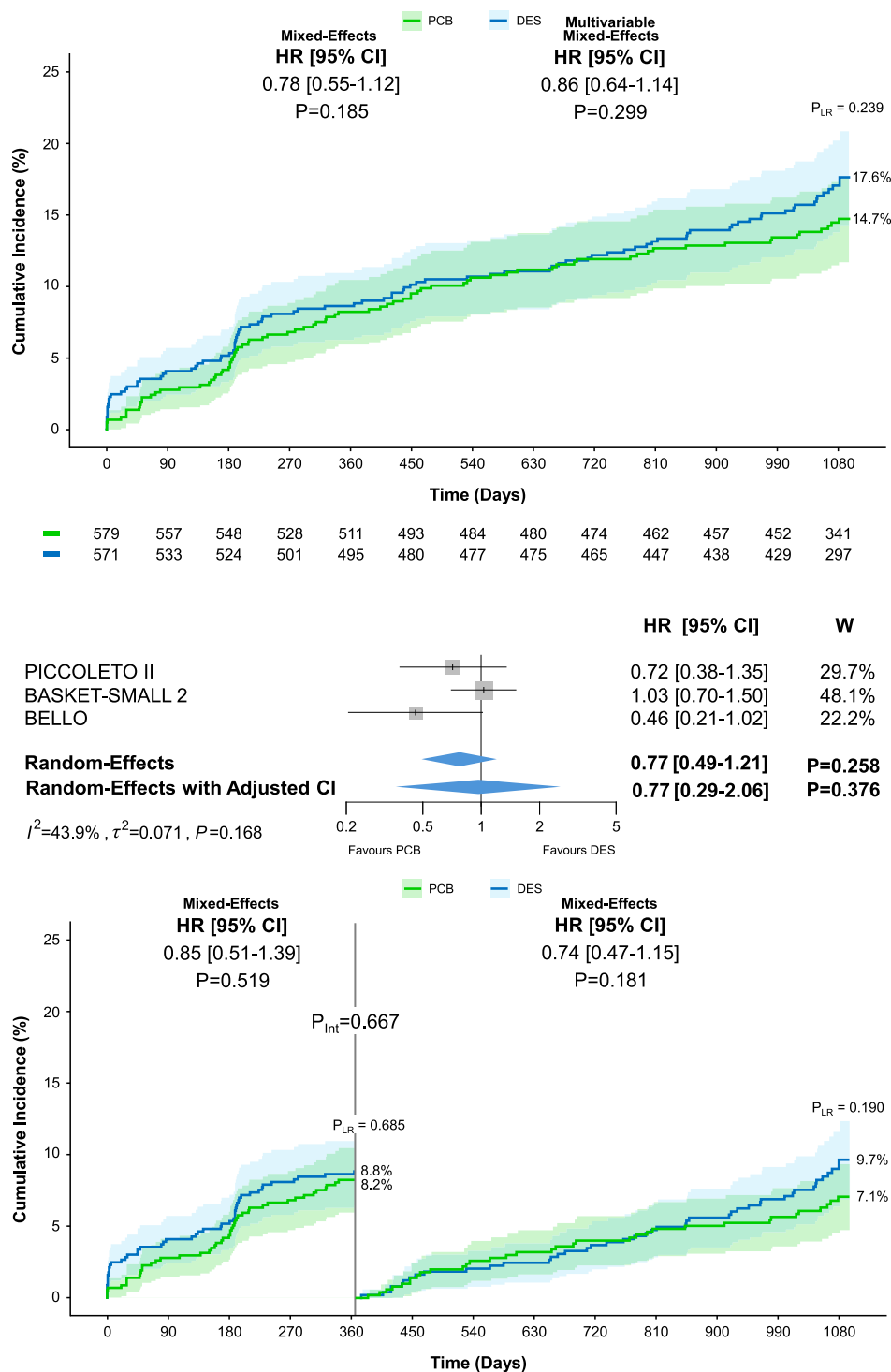
Figure 2 Target lesion failure at 3 year follow-up. Cumulative incidence of the co-primary endpoint of target lesion failure including cardiac death, myocardial infarction, or target lesion revascularization in patients allocated to paclitaxel-coated balloon or drug-eluting stent. The upper panel shows the results of the one-stage analysis on top and the two-stage analysis below. The lower panel displays the landmark analysis performed at 12 months. The numbers of patients at risk between the treatment groups across the time intervals are shown below the graph. P_{int}, *P*-value of the test for interaction; P_{LR}, *P*-value of the log-rank test; W, weight

This result fits the 'leave nothing behind' rationale of PCB angioplasty. The avoidance of permanent metallic implants along with the effective delivery of paclitaxel mitigates several typical histopathologic

mechanisms of DES-based PCI failure such as an exaggerated neointimal proliferation in the first months following PCI, the destabilization of neoatherosclerosis over the years following PCI, and

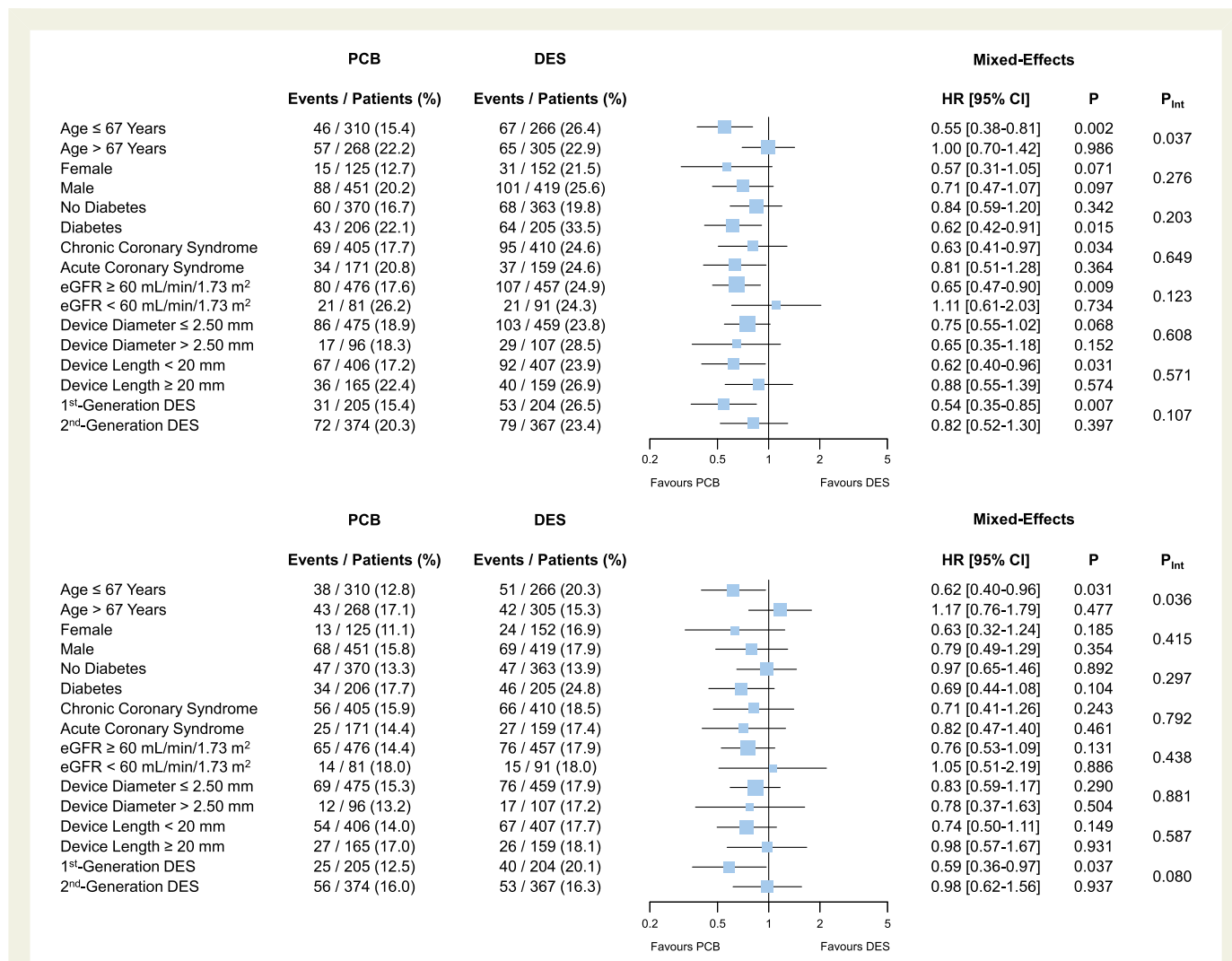|	PCB	DES		Mixed-Effects		
	Events / Patients (%)	Events / Patients (%)		HR [95% CI]	P	P$_{Int}$
Age ≤ 67 Years	46 / 310 (15.4)	67 / 266 (26.4)		0.55 [0.38-0.81]	0.002	0.037
Age > 67 Years	57 / 268 (22.2)	65 / 305 (22.9)		1.00 [0.70-1.42]	0.986	
Female	15 / 125 (12.7)	31 / 152 (21.5)		0.57 [0.31-1.05]	0.071	0.276
Male	88 / 451 (20.2)	101 / 419 (25.6)		0.71 [0.47-1.07]	0.097	
No Diabetes	60 / 370 (16.7)	68 / 363 (19.8)		0.84 [0.59-1.20]	0.342	0.203
Diabetes	43 / 206 (22.1)	64 / 205 (33.5)		0.62 [0.42-0.91]	0.015	
Chronic Coronary Syndrome	69 / 405 (17.7)	95 / 410 (24.6)		0.63 [0.41-0.97]	0.034	0.649
Acute Coronary Syndrome	34 / 171 (20.8)	37 / 159 (24.6)		0.81 [0.51-1.28]	0.364	
eGFR ≥ 60 mL/min/1.73 m^2	80 / 476 (17.6)	107 / 457 (24.9)		0.65 [0.47-0.90]	0.009	0.123
eGFR < 60 mL/min/1.73 m^2	21 / 81 (26.2)	21 / 91 (24.3)		1.11 [0.61-2.03]	0.734	
Device Diameter ≤ 2.50 mm	86 / 475 (18.9)	103 / 459 (23.8)		0.75 [0.55-1.02]	0.068	0.608
Device Diameter > 2.50 mm	17 / 96 (18.3)	29 / 107 (28.5)		0.65 [0.35-1.18]	0.152	
Device Length < 20 mm	67 / 406 (17.2)	92 / 407 (23.9)		0.62 [0.40-0.96]	0.031	0.571
Device Length ≥ 20 mm	36 / 165 (22.4)	40 / 159 (26.9)		0.88 [0.55-1.39]	0.574	
1st-Generation DES	31 / 205 (15.4)	53 / 204 (26.5)		0.54 [0.35-0.85]	0.007	0.107
2nd-Generation DES	72 / 374 (20.3)	79 / 367 (23.4)		0.82 [0.52-1.30]	0.397	

0.2   0.5   1   2   5
Favours PCB   Favours DES

	PCB	DES		Mixed-Effects		
	Events / Patients (%)	Events / Patients (%)		HR [95% CI]	P	P$_{Int}$
Age ≤ 67 Years	38 / 310 (12.8)	51 / 266 (20.3)		0.62 [0.40-0.96]	0.031	0.036
Age > 67 Years	43 / 268 (17.1)	42 / 305 (15.3)		1.17 [0.76-1.79]	0.477	
Female	13 / 125 (11.1)	24 / 152 (16.9)		0.63 [0.32-1.24]	0.185	0.415
Male	68 / 451 (15.8)	69 / 419 (17.9)		0.79 [0.49-1.29]	0.354	
No Diabetes	47 / 370 (13.3)	47 / 363 (13.9)		0.97 [0.65-1.46]	0.892	0.297
Diabetes	34 / 206 (17.7)	46 / 205 (24.8)		0.69 [0.44-1.08]	0.104	
Chronic Coronary Syndrome	56 / 405 (15.9)	66 / 410 (18.5)		0.71 [0.41-1.26]	0.243	0.792
Acute Coronary Syndrome	25 / 171 (14.4)	27 / 159 (17.4)		0.82 [0.47-1.40]	0.461	
eGFR ≥ 60 mL/min/1.73 m^2	65 / 476 (14.4)	76 / 457 (17.9)		0.76 [0.53-1.09]	0.131	0.438
eGFR < 60 mL/min/1.73 m^2	14 / 81 (18.0)	15 / 91 (18.0)		1.05 [0.51-2.19]	0.886	
Device Diameter ≤ 2.50 mm	69 / 475 (15.3)	76 / 459 (17.9)		0.83 [0.59-1.17]	0.290	0.881
Device Diameter > 2.50 mm	12 / 96 (13.2)	17 / 107 (17.2)		0.78 [0.37-1.63]	0.504	
Device Length < 20 mm	54 / 406 (14.0)	67 / 407 (17.7)		0.74 [0.50-1.11]	0.149	0.587
Device Length ≥ 20 mm	27 / 165 (17.0)	26 / 159 (18.1)		0.98 [0.57-1.67]	0.931	
1st-Generation DES	25 / 205 (12.5)	40 / 204 (20.1)		0.59 [0.36-0.97]	0.037	0.080
2nd-Generation DES	56 / 374 (16.0)	53 / 367 (16.3)		0.98 [0.62-1.56]	0.937	

0.2   0.5   1   2   5
Favours PCB   Favours DES

Figure 3 Subgroup analyses for major adverse cardiac event and target lesion failure at 3 year follow-up. Major adverse cardiac event (upper panel) includes all-cause death, myocardial infarction, or target vessel revascularization. Target lesion failure (lower panel) includes cardiac death, myocardial infarction, or target lesion revascularization. After adjusting for repeated statistical testing, the interaction P-value for median age in both analyses was no longer significant (0.296 and 0.288, respectively). P$_{int}$, P-value of the test for interaction

pro-thrombotic conditions such as incomplete stent re-endothelialization.[9,37–39] These possible unfavourable patterns of PCI failure after DES implantation can be responsible for acute myocardial infarction due to in-stent restenosis, vulnerable plaque destabilization in the context of in-stent neoatherosclerosis, and intra-luminal thrombosis triggered by the contact between blood and non-endothelialized metallic struts.[9,37–39] Moreover, PCBs have demonstrated positive late vessel remodelling effects after treatment of de novo lesions in nearly 60% of the cases, often resulting in negligible angiographic late lumen loss.[40–43] This advantageous effect may be particularly beneficial in SV-CAD. The higher rates of restenosis and thrombosis associated with DES implantation may also provide a reasonable explanation for the decreased 3-year incidence of target vessel revascularization in patients assigned to PCB angioplasty (crude absolute rate difference of 4.5%), resulting in a significant difference by one-stage analysis. However, it is also necessary to report that differences were vulnerable to the statistical model used likely

reflecting the need for more data to assess whether PCB angioplasty is superior to DES implantation in treating SV-CAD.

The complementary key conclusion of the ANDROMEDA study is the absence of significant differences between PCB and DES in the co-primary endpoint of TLF, regardless of the model employed. After pooling all available evidence from randomized trials by the inclusion of reconstructed patient-level time-to-event data from the RESTORE SVD China trial, the results remained consistent by both one- and two-stage analyses. In addition, landmark analyses showed similar trends between PCB angioplasty and DES implantation in the periods from PCI to 1 year and 1–3 years, indicating consistent effects over time. Yet, the potential higher biocompatibility associated with PCB angioplasty vs. DES implantation may require a more prolonged observation, and in other settings some signals of improved safety were detected only at a very late follow-up.[44] Additionally, the role of DES generation influenced general conclusions, as we found higher 3-year TLF in patients who received first-generation DES compared with those
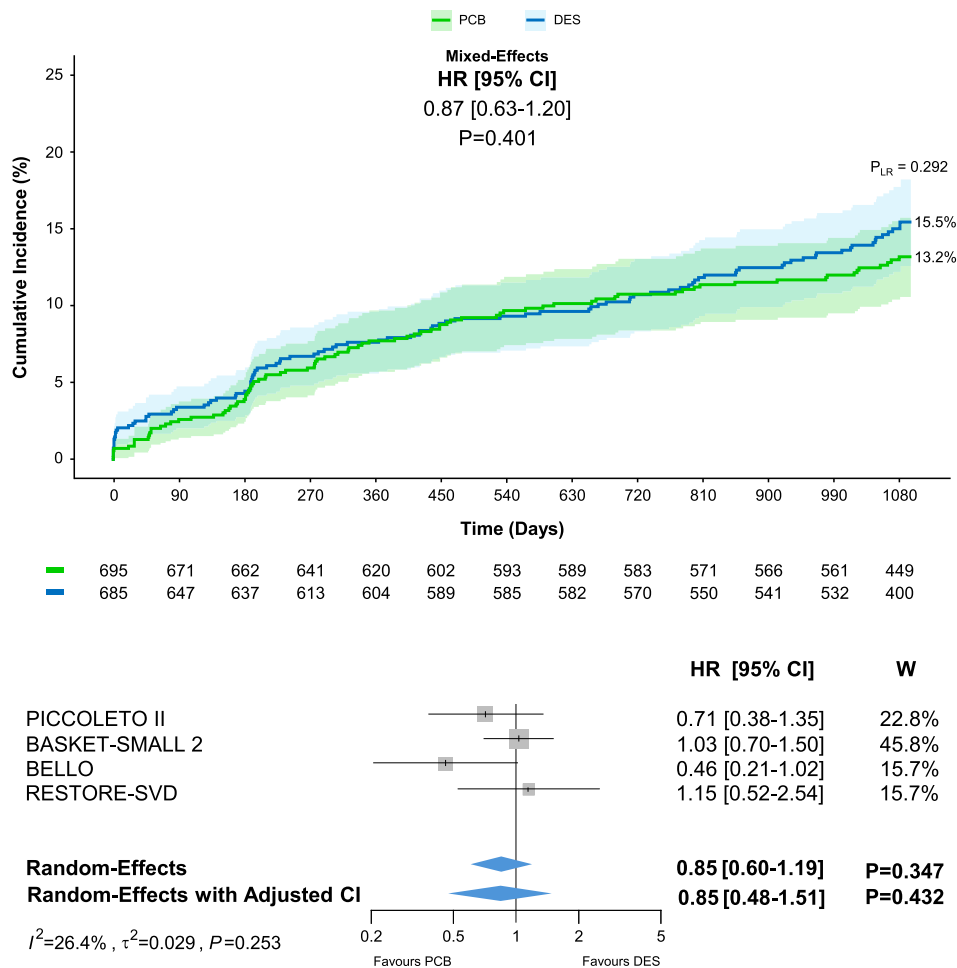
Figure 4 Target lesion failure at 3 year follow-up with inclusion of reconstructed time-to-event individual patient data from the RESTORE SVD China trial. Target lesion failure includes cardiac death, myocardial infarction, or target lesion revascularization. P_{LR}, P-value of the log-rank test; W, weight

who received PCB and second-generation DES. The absence of significant differences in TLF between patients assigned to PCB and those assigned to second-generation DES is another major finding of the ANDROMEDA study.

Some concerns about increased mortality following paclitaxel application in peripheral interventions were raised by a previous meta-analysis.[45] However, more recently, several studies and, updated metanalyses on both peripheral and coronary applications of DCB, have dismissed this initial cause of concern.[20,44,46,47] Our study further confirms no association between all-cause mortality and paclitaxel use in the coronary field, and no significant difference in mortality between the DCB and DES groups.

In the ANDROMEDA study, the assessment of heterogeneity generally showed moderate between-trial differences due to more neutral effects associated with the BASKET-SMALL 2 trial compared with those associated with the BELLO and PICCOLETO II trials. In the comprehensive assessment of the available evidence in terms of 3-year TLF, the RESTORE SVD trial showed effects more consistent with the BASKET-SMALL 2 trial, and the quantification of between-trial differences produced statistics indicating only mild heterogeneity. In addition, a subgroup analysis for MACE and TLF according to median age at the time of PCI showed a significant treatment-by-subgroup interaction. Importantly, regardless of the presence of an interaction, multivariable one-stage analyses including age did not reveal inconsistency compared with standard one-stage analyses.

The recently published REC-CAGEFREE I trial, the largest available randomized clinical comparing PCB angioplasty with rescue stenting vs. intended DES implantation for the treatment of *de novo* any-reference vessel diameter coronary lesions, did not demonstrate non-inferiority of PCB-based PCI compared with DES-based PCI in terms of the primary composite endpoint of cardiovascular death, target vessel myocardial infarction, or clinically or physiologically indicated target lesion revascularization at 2-year follow-up.[48] The difference between treatments was mainly driven by an excess in clinically or physiologically indicated target lesion revascularization.[48] However, a major subanalysis involving patients with SV-CAD (45.4%) showed no significant difference in the primary composite endpoint between the PCB and DES groups (5.1% vs. 4.4%; HR 1.17, 95% CI 0.67–2.05).[48] Of note, the assessment of treatment-by-subgroup interaction with patients without SV-CAD showed a significant effect (*P* = .020), indicating a possible major influence of reference vessel diameter on PCB effectiveness.

Finally, the ANDROMEDA study included only patients undergoing PCB angioplasty. The present results may therefore not apply to sirolimus-coated balloons. Preliminary investigations with this newer class of devices showed mixed conclusions, and ongoing large-scale randomized clinical trials including patients with SV-CAD, such as TRANSFORM II (NCT04893291)[49] and SELUTION (NCT05946629),[50] will provide more conclusive evidence regarding sirolimus-coated balloons.

Limitations

The ANDROMEDA study presents some limitations that should be considered when interpreting the main results. First, except BASKET-SMALL 2, the other available trials involved a 6–9-month angiography follow-up to assess the primary surrogate endpoint.[15–19,33–35] However, in the ANDROMEDA study, landmark analyses showed that the outcomes of MACE and TLF between treatment groups did not significantly differ between the periods before and after 1 year. Second, the definition of SV-CAD showed some differences across trials, with an upper limit of the reference vessel diameter of target lesions ranging from 2.75 to 3.00 mm.[15–19,33–35] Nevertheless, in the ANDROMEDA study, the proportion of patients with reference vessel diameter ≤2.50 mm was predominant (>80%), and subgroup analyses for MACE and TLF showed no significant influence of reference vessel diameter on the outcomes between treatment groups. Third, the use of different DES generations across trials introduced heterogeneity, and it is plausible that some advantages associated with PCB are influenced by the lower effectiveness of first-generation DES. Indeed, 31% of patients assigned to DES across the available trials received a first-generation device. Despite this limitation, the subgroup analyses for MACE and TLF and a comprehensive three-group analysis (PCB, first-generation DES, and second-generation DES) of 3 year TLF did not reveal significant differences between PCB angioplasty and second-generation DES, before and after adjustment for repeated pairwise comparisons. Fourth, a low proportion of patients underwent functionally or intravascular imaging-guided PCI, and a systematic invasive functional assessment of the target lesion would have more robustly outlined the clinical significance of SV-CAD, subtending in some circumstances small ischaemic areas of myocardium.[15–19,33–35] Yet, the setting of SV-CAD involves high proportions of target lesions located in secondary epicardial branches or distal vessel segments in which employing complementary techniques for guiding and optimizing PCI is often challenging or unfeasible.[51,52] Finally, the RESTORE SVD China trial was not fully available due to time restrictions on data transfer. However, we partially overcome this limitation by reconstructing time-to-event individual patient data for TLF from the original Kaplan–Meier curves and performing both one- and two-stage analyses. Of note, the comprehensive pooling of available evidence on PCB angioplasty vs. DES implantation for SV-CAD from randomized trials showed no significant difference between treatment groups.

Conclusions

In patients undergoing PCI for *de novo* SV-CAD, PCB angioplasty is associated at 3 year follow-up with a reduced risk of MACE and a non-significant difference in TLF compared with DES implantation. The restriction of the comparator group to second-generation DES does not alter the main conclusions. Larger trials comparing contemporary devices at a more prolonged follow-up are warranted to assess whether in the setting of SV-CAD DCB angioplasty improves cardiovascular outcomes compared with DES implantation.

Supplementary data

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

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

All authors declare no funding for this contribution.

Ethical Approval

The local institutional review boards approved all included trials at each participating centre, and all patients provided written informed consent before randomization. Clinical events and angiographic measurements in each trial were assessed by independent clinical events committees and core laboratories, respectively.

Pre-registered Clinical Trial Number

ANDROMEDA was registered with PROSPERO (CRD42023479035).

References

1. Simard T, Hibbert B, Ramirez FD, Froeschl M, Chen YX, O'Brien ER. The evolution of coronary stents: a brief review. *Can J Cardiol* 2014;**30**:35–45. https://doi.org/10.1016/j.cjca.2013.09.012
2. Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;**301**:61–8. https://doi.org/10.1056/NEJM197907123010201
3. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, *et al.* 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2022;**145**:e18–114. https://doi.org/10.1161/CIR.0000000000001038
4. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, *et al.* 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;**44**:3720–826. https://doi.org/10.1093/eurheartj/ehad191
5. Jeger RV, Eccleshall S, Wan Ahmad WA, Ge J, Poerner TC, Shin ES, *et al.* Drug-coated balloons for coronary artery disease: third report of the international DCB consensus group. *JACC Cardiovasc Interv* 2020;**13**:1391–402. https://doi.org/10.1016/j.jcin.2020.02.043
6. Yerasi C, Case BC, Forrestal BJ, Torguson R, Weintraub WS, Garcia-Garcia HM, *et al.* Drug-coated balloon for de novo coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:1061–73. https://doi.org/10.1016/j.jacc.2019.12.046
7. Rasanen A, Karkkainen JM, Eranti A, Eranen J, Rissanen TT. Percutaneous coronary intervention with drug-coated balloon-only strategy combined with single antiplatelet treatment in patients at high bleeding risk: single center experience of a novel concept. *Catheter Cardiovasc Interv* 2023;**101**:569–78. https://doi.org/10.1002/ccd.30558
8. Rissanen TT, Uskela S, Eranen J, Mantyla P, Olli A, Romppanen H, *et al.* Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. *Lancet* 2019;**394**:230–9. https://doi.org/10.1016/S0140-6736(19)31126-2
9. Fezzi S, Ding D, Mahfoud F, Huang J, Lansky AJ, Tu S, *et al.* Illusion of revascularization: does anyone achieve optimal revascularization during percutaneous coronary intervention? *Nat Rev Cardiol* 2024;**21**:652–62. https://doi.org/10.1038/s41569-024-01014-0
10. Madhavan MV, Kirtane AJ, Redfors B, Généreux P, Ben-Yehuda O, Palmerini T, *et al.* Stent-related adverse events >1 year after percutaneous coronary intervention. *J Am Coll Cardiol* 2020;**75**:590–604. https://doi.org/10.1016/j.jacc.2019.11.058
11. Kufner S, Ernst M, Cassese S, Joner M, Mayer K, Colleran R, *et al.* 10-year outcomes from a randomized trial of polymer-free versus durable polymer drug-eluting coronary stents. *J Am Coll Cardiol* 2020;**76**:146–58. https://doi.org/10.1016/j.jacc.2020.05.026
12. Cassese S, Byrne RA, Tada T, Pinieck S, Joner M, Ibrahim T, *et al.* Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart* 2014;**100**:153–9. https://doi.org/10.1136/heartjnl-2013-304933

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13. Claessen BE, Smits PC, Kereiakes DJ, Parise H, Fahy M, Kedhi E, *et al.* Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (clinical evaluation of the XIENCE V everolimus eluting coronary stent system) and COMPARE (second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) randomized trials. *JACC Cardiovasc Interv* 2011;**4**:1209–15. https://doi.org/10.1016/j.jcin.2011.07.016

14. van der Heijden LC, Kok MM, Danse PW, Schramm AR, Hartmann M, Löwik MM, *et al.* Small-vessel treatment with contemporary newer-generation drug-eluting coronary stents in all-comers: insights from 2-year DUTCH PEERS (TWENTE II) randomized trial. *Am Heart J* 2016;**176**:28–35. https://doi.org/10.1016/j.ahj.2016.02.020

15. Latib A, Colombo A, Castriota F, Micari A, Cremonesi A, De Felice F, *et al.* A randomized multicenter study comparing a drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (balloon elution and late loss optimization) study. *J Am Coll Cardiol* 2012;**60**:2473–80. https://doi.org/10.1016/j.jacc.2012.09.020

16. Cortese B, Di Palma G, Guimaraes MG, Piraino D, Orrego PS, Buccheri D, *et al.* Drug-coated balloon versus drug-eluting stent for small coronary vessel disease: PICCOLETO II randomized clinical trial. *JACC Cardiovasc Interv* 2020;**13**:2840–9. https://doi.org/10.1016/j.jcin.2020.08.035

17. Tang Y, Qiao S, Su X, Chen Y, Jin Z, Chen H, *et al.* Drug-coated balloon versus drug-eluting stent for small-vessel disease: the RESTORE SVD China randomized trial. *JACC Cardiovasc Interv* 2018;**11**:2381–92. https://doi.org/10.1016/j.jcin.2018.09.009

18. Jeger RV, Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Leibundgut G, *et al.* Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet* 2018;**392**:849–56. https://doi.org/10.1016/S0140-6736(18)31719-7

19. Cortese B, Testa G, Rivero F, Erriquez A, Alfonso F. Long-term outcome of drug-coated balloon vs drug-eluting stent for small coronary vessels: PICCOLETO-II 3-year follow-up. *JACC Cardiovasc Interv* 2023;**16**:1054–61. https://doi.org/10.1016/j.jcin.2023.02.011

20. Scheller B, Vukadinovic D, Jeger R, Rissanen TT, Scholz SS, Byrne R, *et al.* Survival after coronary revascularization with paclitaxel-coated balloons. *J Am Coll Cardiol* 2020;**75**:1017–28. https://doi.org/10.1016/j.jacc.2019.11.065

21. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, *et al.* Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA* 2015;**313**:1657–65. https://doi.org/10.1001/jama.2015.3656

22. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. https://doi.org/10.1136/bmj.l4898

23. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–6. https://doi.org/10.1136/bmj.39489.470347.AD

24. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, *et al.* Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344–51. https://doi.org/10.1161/CIRCULATIONAHA.106.685313

25. Debray TP, Moons KG, van Valkenhoef G, Efthimiou O, Hummel N, Groenwold RH, *et al.* Get real in individual participant data (IPD) meta-analysis: a review of the methodology. *Res Synth Methods* 2015;**6**:293–309. https://doi.org/10.1002/jrsm.1160

26. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model.* New York: Springer, 2000.

27. Quartagno M, Carpenter JR. Substantive model compatible multilevel multiple imputation: a joint modeling approach. *Stat Med* 2022;**41**:5000–15. https://doi.org/10.1002/sim.9549

28. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al.* *Cochrane Handbook for Systematic Reviews of Interventions.* 2nd edn. Chichester, UK: John Wiley & Sons, 2019.

29. Heinze G, Schemper M. A solution to the problem of monotone likelihood in Cox regression. *Biometrics* 2001;**57**:114–9. https://doi.org/10.1111/j.0006-341x.2001.00114.x

30. Riley RD, Debray TPA, Fisher D, Hattle M, Marlin N, Hoogland J, *et al.* Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: statistical recommendations for conduct and planning. *Stat Med* 2020;**39**:2115–37. https://doi.org/10.1002/sim.8516

31. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B* 1995; **57**:289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

32. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan–Meier survival curves. *BMC Med Res Methodol* 2012;**12**:9. https://doi.org/10.1186/1471-2288-12-9

33. Latib A, Ruparelia N, Menozzi A, Castriota F, Micari A, Cremonesi A, *et al.* 3-year follow-up of the balloon elution and late loss optimization study (BELLO). *JACC Cardiovasc Interv* 2015;**8**:1132–4. https://doi.org/10.1016/j.jcin.2015.04.008

34. Jeger RV, Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Weilenmann D, *et al.* Long-term efficacy and safety of drug-coated balloons versus drug-eluting stents for small coronary artery disease (BASKET-SMALL 2): 3-year follow-up of a randomised, non-inferiority trial. *Lancet* 2020;**396**:1504–10. https://doi.org/10.1016/S0140-6736(20)32173-5

35. Tian J, Tang YD, Qiao S, Su X, Chen Y, Jin Z, *et al.* Two-year follow-up of a randomized multicenter study comparing a drug-coated balloon with a drug-eluting stent in native small coronary vessels: the RESTORE Small Vessel Disease China trial. *Catheter Cardiovasc Interv* 2020;**95**:587–97. https://doi.org/10.1002/ccd.28705

36. Scarsini R, Fezzi S, Leone AM, De Maria GL, Pighi M, Marcoli M, *et al.* Functional patterns of coronary disease: diffuse, focal, and serial lesions. *JACC Cardiovasc Interv* 2022;**15**:2174–91. https://doi.org/10.1016/j.jcin.2022.07.015

37. 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**:3320–31. https://doi.org/10.1093/eurheartj/ehv511

38. Byrne RA, Kastrati A. Prognosis after revascularization for left main coronary artery disease: insights from the crystal ball. *Eur Heart J* 2015;**36**:1212–5. https://doi.org/10.1093/eurheartj/ehv062

39. Alfonso F, Coughlan JJ, Giacoppo D, Kastrati A, Byrne RA. Management of in-stent restenosis. *EuroIntervention* 2022;**18**:e103–23. https://doi.org/10.4244/EIJ-D-21-01034

40. Ahmad WAW, Nuruddin AA, Abdul Kader MASK, Ong TK, Liew HB, Ali RM, *et al.* Treatment of coronary de novo lesions by a sirolimus- or paclitaxel-coated balloon. *JACC Cardiovasc Interv* 2022;**15**:770–9. https://doi.org/10.1016/j.jcin.2022.01.012

41. Ninomiya K, Serruys PW, Colombo A, Reimers B, Basavarajaiah S, Sharif F, *et al.* A prospective randomized trial comparing sirolimus-coated balloon with paclitaxel-coated balloon in de novo small vessels. *JACC Cardiovasc Interv* 2023;**16**:2884–96. https://doi.org/10.1016/j.jcin.2023.09.026

42. Serruys PW, Tobe A, Ninomiya K, Garg S, Finn AV, Scheller B, *et al.* Editorial: is the axiom of balloon angioplasty, "the more you gain the more you lose", still true in the era of DCB with paclitaxel? *Cardiovasc Revasc Med* 2024;**69**:70–8. https://doi.org/10.1016/j.carrev.2024.04.001

43. Fezzi S, Huang J, Lunardi M, Ding D, Ribichini F, Tu S, *et al.* Coronary physiology in the catheterisation laboratory: an A to Z practical guide. *AsiaIntervention* 2022;**8**:86–109. https://doi.org/10.4244/AIJ-D-22-00022

44. Giacoppo D, Alvarez-Covarrubias HA, Koch T, Cassese S, Xhepa E, Kessler T, *et al.* Coronary artery restenosis treatment with plain balloon, drug-coated balloon, or drug-eluting stent: 10-year outcomes of the ISAR-DESIRE 3 trial. *Eur Heart J* 2023;**44**:1343–57. https://doi.org/10.1093/eurheartj/ehad026

45. 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. https://doi.org/10.1161/JAHA.118.011245

46. Sanz Sánchez J, Chiarito M, Cortese B, Moretti A, Pagnotta P, Reimers B, *et al.* Drug-coated balloons vs drug-eluting stents for the treatment of small coronary artery disease: a meta-analysis of randomized trials. *Catheter Cardiovasc Interv* 2021;**98**:66–75. https://doi.org/10.1002/ccd.29111

47. Giacoppo D, Alfonso F, Xu B, Claessen B, Adriaenssens T, Jensen C, *et al.* 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**:3715–28. https://doi.org/10.1093/eurheartj/ehz594

48. Gao C, He X, Ouyang F, Zhang Z, Shen G, Wu M, *et al.* Drug-coated balloon angioplasty with rescue stenting versus intended stenting for the treatment of patients with de novo coronary artery lesions (REC-CAGEFREE I): an open-label, randomised, non-inferiority trial. *Lancet* 2024;**404**:1040–50. https://doi.org/10.1016/S0140-6736(24)01594-0

49. Greco A, Sciahbasi A, Abizaid A, Mehran R, Rigattieri S, de la Torre Hernandez JM, *et al.* Sirolimus-coated balloon versus everolimus-eluting stent in de novo coronary artery disease: rationale and design of the TRANSFORM II randomized clinical trial. *Catheter Cardiovasc Interv* 2022;**100**:544–52. https://doi.org/10.1002/ccd.30358

50. Spaulding C, Krackhardt F, Bogaerts K, Urban P, Meis S, Morice MC, *et al.* Comparing a strategy of sirolimus-eluting balloon treatment to drug-eluting stent implantation in de novo coronary lesions in all-comers: design and rationale of the SELUTION DeNovo trial. *Am Heart J* 2023;**258**:77–84. https://doi.org/10.1016/j.ahj.2023.01.007

51. Escaned J, Berry C, De Bruyne B, Shabbir A, Collet C, Lee JM, *et al.* Applied coronary physiology for planning and guidance of percutaneous coronary interventions. A clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the European Society of Cardiology. *EuroIntervention* 2023;**19**:464–81. https://doi.org/10.4244/EIJ-D-23-00194

52. Giacoppo D, Laudani C, Occhipinti G, Spagnolo M, Greco A, Rochira C, *et al.* Coronary angiography, intravascular ultrasound, and optical coherence tomography for guiding of percutaneous coronary intervention: a systematic review and network meta-analysis. *Circulation* 2024;**149**:1065–86. https://doi.org/10.1161/CIRCULATIONAHA.123.067583