Drug coated balloons versus drug eluting stents for de novo coronary artery disease: a systematic review and meta-analysis of randomised controlled trials

Natasha Corballis,[a,b] Rajkumar Natarajan,[a,b] Ioannis Merinopoulos,[a,b] Vasiliki Tsampasian,[a,b] Allan Clark,[a] Simon Eccleshall,[b,c] and Vassilios S. Vassiliou[a,b,*,c]

[a]Bob Champion Research and Education, Norwich Medical School, University of East Anglia, Rosalind Franklin Road, NR4 7UQ, UK
[b]Department of Cardiology, Norfolk and Norwich University Hospital NHS Foundation Trust, Colney Lane, Norwich, NR4 7LJ, UK

eClinicalMedicine 2026;■: 104204
Published Online XXX
https://doi.org/10.1016/j.eclinm.2026.104204

Summary

Background Drug coated balloon (DCB) only percutaneous coronary intervention (PCI) has an established evidence base in small vessel de novo disease, but recent randomised studies have investigated its use across a broader spectrum of coronary disease. We systematically reviewed randomised evidence comparing DCB with drug eluting stent (DES) PCI for de novo coronary disease.

Methods This systematic review and meta-analysis was conducted in line with the PRISMA statement. PubMed, Scopus, and Embase were systematically searched from inception until 30th May 2026 for randomised trials comparing DCB with DES PCI for de novo coronary disease. Principal outcomes were cardiovascular death, myocardial infarction (MI) and revascularisation. Random-effects models generated odds ratios with 95% confidence intervals. Heterogeneity was assessed using I^2 and publication bias by visual inspection of funnel plots. Risk of bias was assessed using Cochrane RoB2. This study was prospectively registered with PROSPERO (CRD420251167202).

Findings Ten RCTs including 7832 patients were identified. There was no significant difference between DCB and DES in cardiovascular death [OR 1.06 (0.75–1.49), p = 0.76, I^2 = 0%] or MI [OR: 1.02 (0.76–1.36), p = 0.91, I^2 = 0%]. These findings remained consistent after excluding small-vessel-only trials. Revascularisation did not differ across all trials [OR 1.39 (0.88, 2.20), p = 0.16, I^2 = 57%] but was higher with DCB after excluding small-vessel-only trials [OR 1.84 (1.06–3.19), p = 0.03, I^2 = 54%]. This finding was sensitive to exclusion of REC-CAGEFREE I. Visual inspection of funnel plots did not suggest substantial publication bias.

Interpretation DCB and DES strategies had comparable rates of cardiovascular death and MI across the studied de novo coronary populations. The higher revascularisation rates observed after excluding small-vessel-only trials requires cautious interpretation given between-study heterogeneity and sensitivity to one trial. Further adequately powered RCTs with longer follow-up are required to establish the efficacy of DCB strategies in large vessels and more complex coronary lesions.

Funding No funding was received for this study.

Copyright © 2026 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Drug-coated balloon; Drug eluting stent; Percutaneous coronary intervention

Introduction

Whilst drug coated balloons (DCB) are an established and guideline recommended treatment strategy for instent restenosis,[1,2] their use for de novo coronary artery disease remains an active area of investigation. There has been a growing body of evidence supporting their non-inferiority in the role of small vessel de novo disease[3–8] with a recent patient level meta-analysis showing a reduction in major adverse cardiovascular events (MACE) when using a DCB compared to a drug eluting stent (DES) in small vessel disease,[9] which is expected to influence future interventional guidelines.

*Corresponding author. Norwich Medical School, Norwich, NR4 7UQ, UK.
E-mail address: v.vassiliou@uea.ac.uk (V.S. Vassiliou).
[c]Contributed equally.

Research in context

Evidence before this study

We performed a preliminary search of PubMed and the Cochrane library from inception to 1st May 2026 for existing systematic reviews and meta-analyses exploring the use of drug coated balloons or drug eluting stents in de novo coronary disease. The search terms 'drug coated balloons', 'drug-eluting stents', 'de novo coronary artery disease' and 'meta-analysis' were used. Previous evidence included a patient-level meta-analysis showing a significant reduction in major adverse cardiovascular events in patients with small vessel coronary disease and a meta-analysis evaluating DCB versus DES across a broader range of vessel sizes. However, the latter preceded publication of SELUTION De Novo trial. Therefore, the contemporary randomised evidence comparing DCB and DES strategies across the broader spectrum of de novo coronary artery disease had not yet been comprehensively synthesised.

Added value of this study

This study incorporates the most recently published randomised controlled trials comparing DCB to DES for de novo disease and adds an important analysis excluding small vessel-only studies looking at cardiovascular death, myocardial infarction (MI) and target lesion/vessel revascularisation. Importantly, it shows no difference in cardiovascular death or MI, even when excluding small vessel-only studies. There is however a significant increase in TLR with DCB when excluding small vessel-only studies. It is also a comprehensive meta-analysis on the topic, including over 7000 patients and 10 RCTs.

Implications of all the available evidence

Available randomised evidence suggests comparable rates of cardiovascular death and myocardial infarction with DCB and DES strategies for de novo coronary artery disease, including in studies not restricted to small vessels. However, uncertainty remains about repeat revascularisation, particularly in larger vessels, and differences between DCB platforms mean that a class effect should not be assumed. Further adequately powered randomised trials with longer-term follow-up are needed to establish the efficacy of DCB strategies in larger vessels and complex coronary lesions.

However, until recently, there has been a paucity of randomised data on the use of DCB in all-comer de novo coronary disease. Whilst registry data has suggested efficacy and safety in a number of clinical settings such as bifurcations,[10] STEMI[11] and multivessel disease,[12] and evidence supporting a return to physiological vasomotor function after DCB,[13] large head to head trials comparing DCB with DES have been lacking. With the recent publication of two large clinical trials, we sought to conduct an up to date meta-analysis to investigate the safety and efficacy of DCB compared to DES in de novo coronary disease looking at hard clinical endpoints.

Methods

Search strategy and selection criteria

Pubmed, Embase, and Scopus were systematically searched for studies investigating clinical outcomes when using DCB-only versus DES-only PCI to treat de novo coronary disease, from inception to 30th May 2026. The full search strategy is delineated in the Supplementary Material (Supplementary Table S1). The inclusion criteria were: 1) Randomised controlled trials, 2) peer reviewed articles, 3) de novo coronary disease, 4) DCB-only versus DES-only, 5) second generation minimum DES, 6) any vessel size, and 7) minimum of 12 months follow-up. The exclusion criteria included instent restenosis studies, studies that involved a hybrid stategy, and non-randomised study design. One study, Basket-Small 2, used predominantly 2nd generation DES in the comparator arm and was therefore included in the analysis as the comparator arm largely comprised contemporary DES platforms and remained consistent with the clinical question.

Data extraction

Search findings were imported for abstract screening into Covidence.[14] Duplicates were removed and abstracts were screened independently by two researchers (NC and RN). Any conflicts were resolved by a third researcher (VV). All abstracts meeting the inclusion criteria were identified for full text review with data then extracted for the included studies by two researchers independently (NC and RN). Supplementary Table S2 outlines the full-text exclusions and reason for exclusion.

Outcomes

Given significant heterogeneity in the trial-level definition of major adverse cardiovascular events (MACE), individual components of cardiovascular death, myocardial infarction and target lesion/vessel revascularisation were identified as the principal outcomes of interest. For revascularisation outcomes, TLR was extracted preferentially. Where TLR was not reported, TVR was used as the closest available revascularisation endpoint to maximise study inclusion. Given the distinction between lesion- and vessel-level revascularisation, sensitivity analyses were performed restricted to studies reporting TLR. Analyses were undertaken with all studies and excluding small vessel-only studies as well as ACS-only studies/data. The individual trial definitions have been outlined in Supplementary Tables S3 and S4. Outcomes were analysed using the longest

available reported follow-up for each study. Follow-up ranged from 12 to 60 months across the included trials (Supplementary Table S3).

For the purpose of this review, the intervention was defined as DCB or DES. Bailout stenting was permitted according to the protocol of the individual studies and was included within the DCB arm, as part of an intention-to-treat primary analysis.

Statistical analysis

Quantitative synthesis of the included studies was undertaken using Review Manager (Version 5.3 Copenhagen: The Cochrane Collaboration). Analyses were based on trial level event counts, with treatment effects expressed as odds ratios (OR) with 95% confidence intervals CIs). OR rather than time-to-event estimates were used because hazard ratios were not consistently reported across the included studies. Random effects models with inverse variance weightings were selected for use *a priori* because clinical and methodological heterogeneity between trials were anticipated, including differences in patient populations, lesion characteristics, DCB platforms and follow-up duration. Statistical significance was set at $p < 0.05$.

Between trial heterogeneity was examined using I^2 statistics with significant heterogeneity determined at >50%. Publication bias was assessed qualitatively by visual inspection of inverted funnel plot asymmetry. Formal statistical testing funnel plot asymmetry was not performed given the limited number of included studies.

The primary analyses (cardiovascular death, myocardial infarction, revascularisation, and target lesion thrombosis), analyses excluding small-vessel-only studies and ACS subgroup analyses were prespecified. Several additional post-hoc analyses were undertaken during peer review to assess robustness of the findings and explore potential sources of heterogeneity. These comprised leave-one-out sensitivity analyses for individual studies and endpoints, including assessment of the influence of the DCB platform and drug; sensitivity analyses restricted to studies reporting TLR rather than target vessel revascularisation; sensitivity analyses excluding studies with some concern on RoB2 assessment; subgroup analyses comparing studies restricted to small-vessel-only disease with those enrolling non-small-vessel-only disease, with formal testing for subgroup interaction; and sensitivity analysis for revascularisation outcomes according to follow-up duration (12 months versus ≥24 months).

Bias assessment

The Cochrane Risk of Bias assessment tool (RoB 2)[15] was used to identify quality of included papers for the RCTs, covering five domains: 1) the randomisation process, 2) deviations from the intended interventions, 3) missing outcome data, 4) measurement of the outcome, and 5) selection of the reported result. The reliability of results for each outcome was assessed using the GRADE system[16] (Supplementary Table S5). This was screened independently by two researchers (NC and RN). Any conflicts were reviewed by a third researcher (VV).

Ethics

Ethical approval was not required for this systematic review and meta-analysis because the study used only aggregate data from previously published studies and involved no new collection of individual participant data. Consequently, separate written informed consent was not required for this meta-analysis; consent and ethical approval were the responsibility of the investigators of original included studies. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and in accordance with the principles of the Declaration of Helsinki.[17] The meta-analysis was registered with PROSPERO (CRD420251167202).

Role of the funding source

No funding was received for this work.

Results

The search of Pubmed, Embase, Scopus, and relevant references yielded a total of 2948 results, of which 438 duplicates were excluded. From this, 2510 abstracts were screened at title and abstract level, before 29 studies underwent full text assessment. Subsequently, 10 studies and 7832 patients met the inclusion criteria and were included in the meta-analysis[3,5–8,18–26] (Fig. 1) (Supplementary Table S2). No potentially eligible non-English language studies were identified during screening.

Table 1 summarises the study design and population cohorts of the included studies.

Four of the included studies are small-vessel disease only.[3,7,8,20,23] Three studies included were only ACS studies,[19,24,25] with sub-group analysis data available for ACS patients for a further three studies.[21,27] Both REC-CAGE FREE I and SELUTION De Novo[28] are large, all-comer trials including all vessel sizes and ACS/CCS clinical presentations although REC-CAGE FREE I was defined as non-complex lesions.[21,29] All comparator arms included a second generation or more novel DES and there was a significant range in the DCB used, with only the Sequent Please (B. Braun) balloon used in more than one RCT. SELUTION De Novo was the only trial involving a sirolimus drug eluting balloon.[28] The Risk of Bias assessment (Supplementary Figure S1) showed 7 studies with low risk of bias across all categories, three studies had some concern in 1–2 domains and one study had some concern in more than 2 domains. GRADE assessment of the certainty of evidence is presented in Supplementary Table S5, yielding moderate certainty for cardiovascular death and

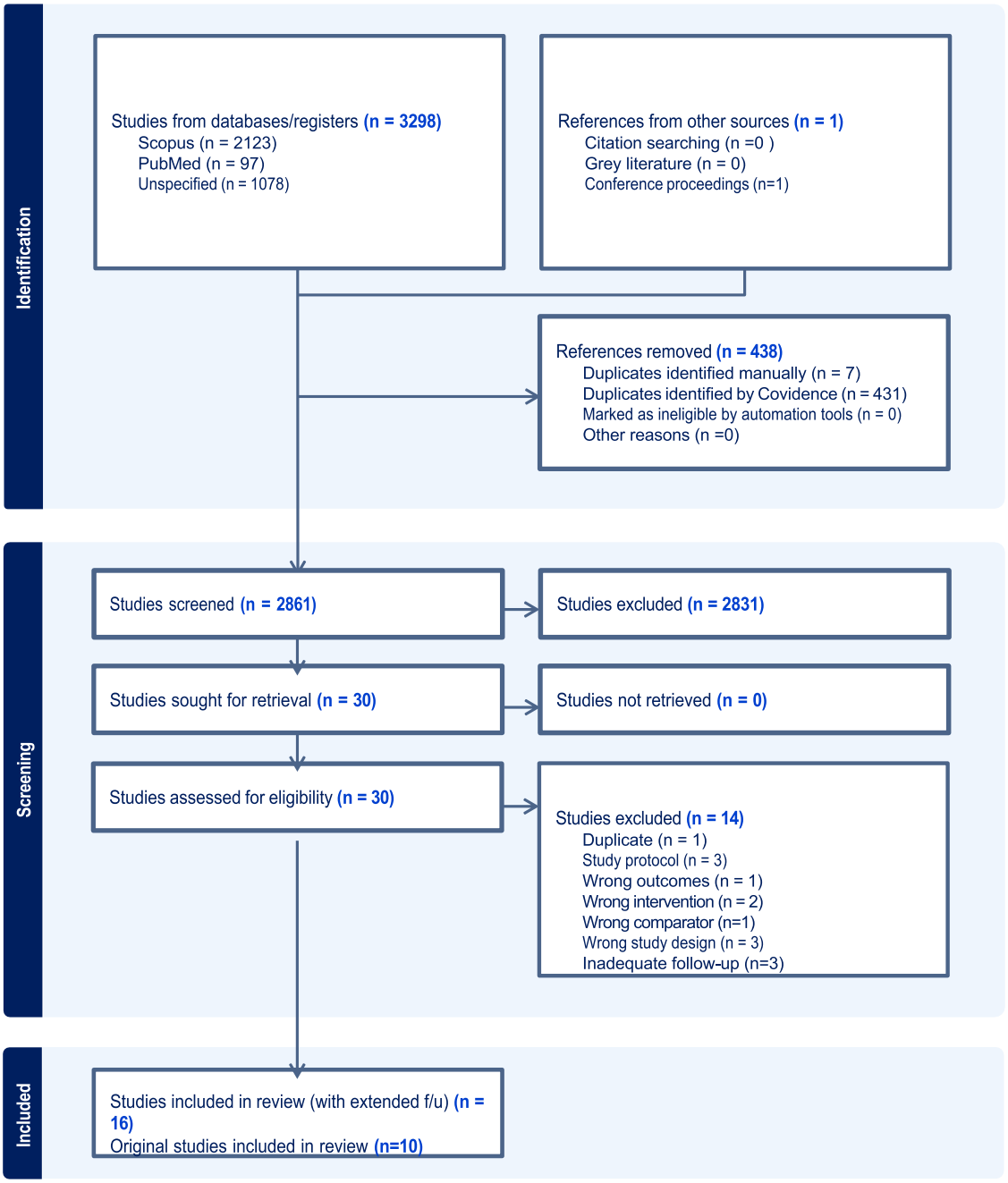


Fig. 1: Study profile. PRISMA flow diagram showing identification, screening, eligibility assessment, and inclusion of studies in the systematic review and meta-analysis. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

myocardial infarction, and low certainty for target lesion/vessel revascularisation. Visual inspection of funnel plots did not suggest substantial asymmetry (Supplementary Figures S2A–C).

There was no significant difference in the occurrence of cardiovascular death whether undergoing DCB or DES treatment [OR: 1.06 (0.75–1.49), p = 0.76], I^2 = 0% (Fig. 2A). Given the growing body of evidence supporting DCB-only PCI in small vessel disease, we subsequently examined occurrence of cardiovascular death in all-comer vessel size, excluding those limited to small vessel disease only. This showed there was still no difference in cardiovascular death [OR: 1.01 (0.68–1.51), p = 0.95], I^2 = 0% (Fig. 2B).

Study (reference)	Population/ design	NDCB/ DES	Study details	DCB/DES	Clinical presentation	Endpoints/follow-up	Age	Male	Prior MI	Prior PCI	Diabetes	EF	RVD	Bailout stenting
BASKET-SMALL-2 [5,23]	Small-vessel de novo; non-inferiority	382/ 376	2018/2020; recruited 2012–2017; Europe; 14 centres	SeQuent please (paclitaxel)/Taxus element (paclitaxel), Xience (everolimus)	ACS, CCS, silent ischaemia	Primary: MACE Secondary: CD, MI, TVR, TV thrombosis, major bleeding Follow-up: 36 mo	67.2 (10.3), 68.4 (10.3)	295 (77), 262 (70)	160 (42), 133 (35)	235 (62), 241 (64)	122 (32), 130 (35)	60 (50–60), 50 (55–65)	2.75 (2.14), 2.57 (0.25)	19 (5.1)
RESTORE-SVD [8]	Small-vessel de novo; non-inferiority	116/ 114	2019; recruited 2016–2017; China; 12 centres	Restore DCB (paclitaxel)/Resolute integrity DES	ACS/CCS	Primary: LLL/TLF Follow-up: 24 mo	60.1 (10.5), 60.5 (10.8)	77 (66.4), 88 (77)	26 (22.4), 28 (24.6)	45 (38.8), 38 (33.3)	46 (39.7), 48 (42.1)	60.6 (7.3), 59.9 (6.9)	2.42 (0.15), 2.42 (0.18)	6 (5.2)
REVELATION [18,19]	Any vessel size; STEMI; non-inferiority	60/60	2019/2022; recruited 2014–2017; Netherlands; 1 centre	Pantera lux (paclitaxel)/3rd-generation DES	STEMI	Primary: FFR Secondary: MACE Follow-up: 60 mo	57.4 (9.2), 57.3 (8.3)	52 (87), 52 (87)	NR	2 (3), 0 (0)	8 (13), 4 (7)	57.1 (6.2), 58.4 (7.1)	NR	11 (18)
PICCOLETO II [6,20]	Small-vessel de novo; non-inferiority	118/ 114	2020/2023; recruited 2015–2018; Europe; 5 centres	Elutax SV (paclitaxel)/ Xience (everolimus)	ACS, CCS	Primary: LLL 6/12, MACE Secondary: components of MACE Follow-up: 36 mo	64 (48–80), 66 (50–82)	83 (70.3), 87 (76.9)	45 (38), 34 (30)	59 (50), 60 (53)	45 (38), 40 (35.4)	58 (48–68), 58 (51–65)	2.23 (0.4), 2.18 (0.4)	8 (6.7)
Yu et al. [26]	Any vessel size; non-inferiority	85/85	2021; recruited 2017–2018; China; 1 centre	SeQuent please (paclitaxel)/Resolute integrity (zotarolimus)	ACS/CCS	Primary: LLL 9/12 Secondary: MACE Follow-up: 12 mo	62.6 (8.8), 64 (10.5)	62 (73.8), 56 (70.9)	NR	11 (13.1), 14 (17.7)	16 (19), 23 (29.1)	NR	2.75 (2.5–3), 3 (2.75–3.5)	2 (2.4)
Hao et al. [25]	Any vessel size; acute MI; RCT	38/42	2021; recruited 2018–2019; China; 1 centre	Yinyi biotech bingo/ Not reported	STEMI	Primary: cardiac death, TV MI, TLR Follow-up: 12 mo	59 (11), 56 (11)	30 (75), 35 (82)	NR	NR	10 (28), 15 (35)	48 (11), 45 (8)	NR	4/42 (9.5)
Wang et al. [24]	STEMI (heavy thrombus burden); non-inferiority	92/92	2022; recruited 2017–2019; China; centres NR	Vasoguard DCB (paclitaxel)/Cordimax stent (sirolimus)	STEMI (heavy thrombus load)	Primary: LLL 9/12 Secondary: MACE Follow-up: 12 mo	49.2 (10.6), 49.6 (8.8)	88 (95.7), 84 (91.3)	NR	NR	71 (77.2), 79 (85.9)	NR	3.31 (0.56), 3.43 (0.48)	NR
DISSOLVE SVD [7]	Small-vessel de novo; non-inferiority	129/ 118	2024; recruited 2018–2019; China; 10 centres	Dissolve DCB (paclitaxel)/Endeavour resolute (zotarolimus)	ACS, CCS	Primary: % diameter stenosis 9/12 Secondary: TLF, TLR, TVF, MACCE Follow-up: 12 mo	60.2 (9.5), 60.1 (9.3)	94 (72.9), 82 (69.5)	33 (25.6), 27 (22.9)	NR	46 (35.7), 45 (38.1)	62.4 (7.8), 61.7 (7.8)	2.20 (0.26), 2.21 (0.24)	5 (3.9)
REC-CAGEFREE I [21,29]	Any vessel size; non-complex lesions; non-inferiority	1133/ 1139	2024; recruited 2021–2022; China; 43 centres	Swide DCB (paclitaxel)/ Firebird 2 DES (sirolimus)	ACS, CCS	Primary: DoCE (CVD, TVMI, TLR) Secondary: all-cause death, stroke, any MI, any revascularisation Follow-up: 36 mo	62 (55–69), 62 (54–69)	769 (67.9), 805 (70.7)	81 (7.1), 105 (9.2)	137 (12.1), 142 (12.5)	282 (24.9), 338 (29.7)	60 (56–65), 60 (56–65)	3 (2.75–3.5), 3 (2.75–3.5)	106 (9.4)
SELUTION De Novo [28]	Any vessel size; non-inferiority	1661/ 1662	2026; Europe and Asia; 62 centres	SELUTION SLR (sirolimus)/DES not specified	ACS, CCS	Primary: TLF Secondary: components of TLF Follow-up: 12 mo	67.1 (9.7), 66.7 (10.4)	1251 (75.3), 1230 (74)	302 (18.2), 284 (17.7)	457 (27.5), 450 (27.1)	425 (25.6), 434 (26.1)	NR	3.1 (0.5), 3.1 (0.5)	NR

Data are presented as DCB, DES unless otherwise specified. ACS, acute coronary syndrome; CCS, chronic coronary syndrome; CD, cardiac death; CVD, cardiovascular death; DCB, drug-coated balloon; DES, drug-eluting stent; DoCE, device-oriented composite endpoint; EF, ejection fraction; FFR, fractional flow reserve; LLL, late lumen loss; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; RVD, reference vessel diameter; STEMI, ST-elevation myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularisation; TV, target vessel; TVF, target vessel failure; TVMI, target vessel myocardial infarction; TVR, target vessel revascularisation.

Table 1: **The study characteristics of the included studies.**

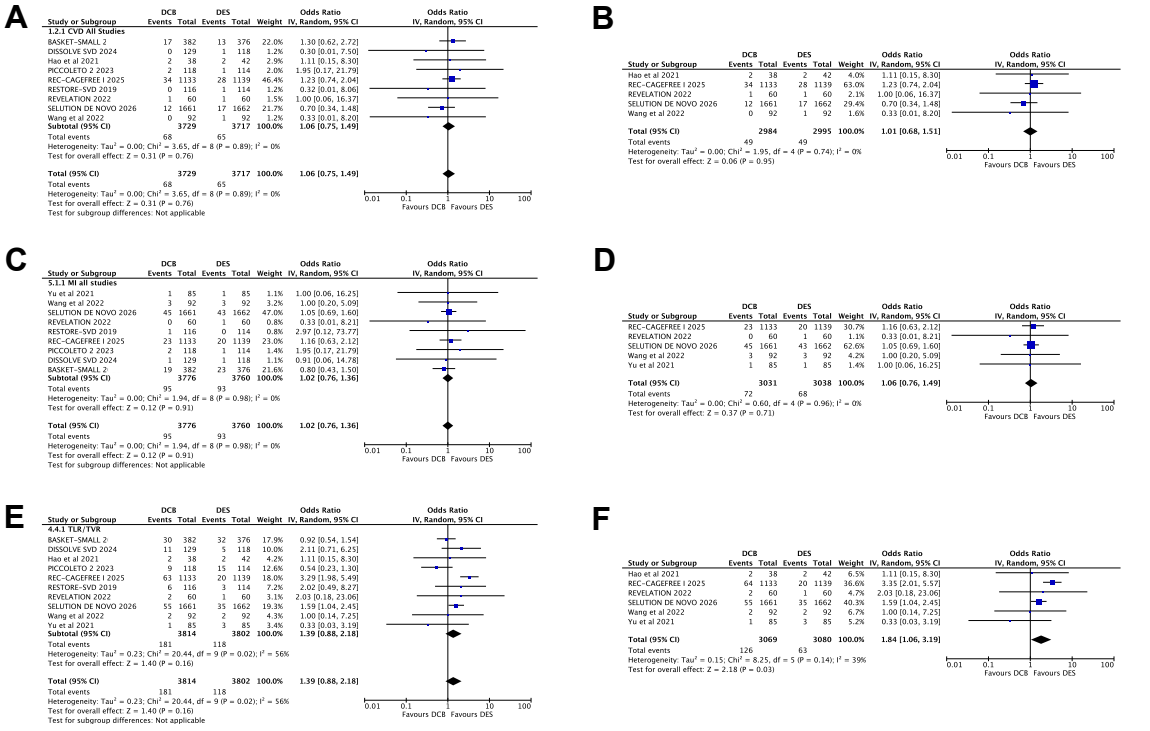


Fig. 2: Forest plots of cardiovascular death, myocardial infarction, and target lesion revascularisation across all studies and when excluding small vessel-only studies. (A) Cardiovascular death across all studies, (B) cardiovascular death excluding small-vessel-only studies, (C): myocardial infarction across all studies, (D) myocardial infarction excluding small-vessel-only studies, (E) revascularisation across all studies, and (F) revascularisation excluding small-vessel-only studies. Effect estimates are presented with odds ratios with 95% confidence intervals. CI, confidence intervals; DCB, drug coated balloon; DES, drug eluting stent; IV, inverse variance; MI, myocardial infarction; OR, odds ratio; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

Sensitivity analyses when analysing ACS-only studies and excluding ACS studies showed there remained no difference in rates of cardiovascular death (Supplementary Figures S3 and S4).

There was no significant difference in the occurrence of MI (target vessel MI where reported) whether undergoing DCB or DES treatment [OR: 1.02 (0.76–1.36), p = 0.91], I^2 = 0% (Fig. 2C). Furthermore, when excluding small vessel-only studies, there remained no significant difference in the rates of myocardial infarction [OR: 1.06 (0.76–1.49), p = 0.71], I^2 = 0% (Fig. 2D).

Additional leave-one-out sensitivity analyses were performed with the non-small-vessel trial cohort to assess the influence of the two largest studies, REC-CAGEFREE I and SELUTION De Novo.[28] Exclusion of either study did not materially alter the pooled estimates for cardiovascular death or myocardial infarction, supporting the robustness of the finding (Supplementary Table S6 and S7).

There was no significant difference in occurrence of target lesion (or target vessel where TLR was not available) revascularisation between the two groups [1.39 (0.88, 2.20), p = 0.16], I^2 = 57% (Fig. 2E). However, when excluding small vessel-only studies, there was a significant increase in TLR in DCB-only compared to DES-only studies [1.84 (1.06–3.19), p = 0.03], I^2 = 54% (Fig. 2F). However, a leave-one-out sensitivity analysis resulted in significant changes in the findings (when removing REC-CAGEFREE I trial resulted in no significant difference between the two treatment strategies) (Supplementary Table S8 and Supplementary Figure S5).

Furthermore, a sensitivity analysis restricted to studies reporting TLR demonstrated findings consistent with the primary revascularisation analysis, supporting the robustness of the pooled estimate variation in revascularisation endpoints (Supplementary Figure S6).

Analysis of MACE in studies either designed for ACS patients only or that reported ACS-only subgroup analyses was undertaken. Given the limited availability of individual endpoint data in ACS subgroup analyses, an exploratory analysis was performed in ACS populations. The individual MACE definitions have been outlined in Supplementary Table S9. This showed no significant difference in MACE between the two treatment groups [OR: 1.07(0.79–1.46), p = 0.66], I^2 = 0% (Supplementary Figure S7).

A further safety analysis of target lesion thrombosis was undertaken. This was reported in 6 studies (7326 patients) and whilst showing no statistical difference, did numerically favour DCB treatment [OR: 0.54 (0.25–1.17), p = 0.12], I^2 = 0% (Supplementary Figure S8).

Leave-one-out analyses demonstrated that exclusion of any individual study did not materially alter the direction or significance of the pooled estimates of the endpoints of interest. Exclusion of the sole sirolimus-eluting balloon trial similarly yielded consistent findings, suggesting that the overall results were not driven by a specific DCB platform or antiproliferative agent (Supplementary Table S10 and S11).

The impact of study quality on pooled estimates was also explored by conducting a sensitivity analysis by excluding studies considered to have some concern or high risk of bias, based on the risk of bias assessment. This showed that the findings were consistent with the primary analysis (Supplementary Table S12). Subgroup analyses stratified according to studies restricted to small-vessel disease and studies enrolling non-small-vessel populations were performed. No significant interaction according to vessel-size subgroup was observed for cardiovascular death or myocardial infarction. Although the point estimate for revascularisation outcomes appeared numerically higher in non-small-vessel studies, formal testing demonstrated no significant subgroup interaction (p-interaction = 0.36; Supplementary Figures S9–S11). Finally, a sensitivity analysis of TLR/TVR based on follow-up duration was undertaken for all studies (Supplementary Figure S12). This demonstrated that up to twelve-month follow-up, there was a significant increase in TLR/TVR with DCB, but this effect was no longer observed at ≥24-month follow-up. Study data for Piccoleto II and Revelation were obtained from the separately published follow-up duration for this sensitivity analysis.

Discussion

This systematic review and meta-analysis of ten randomised controlled trials, involving 7832 patients provides the most contemporary synthesis of evidence comparing DCB-only with DES-only PCI for de novo coronary artery disease. The principal findings are as follows:

1) There was no difference in cardiovascular death, myocardial infarction or treated lesion thrombosis irrespective of vessel size
2) Although there was no difference in revascularisation across all studies, exclusion of small vessel-only trials demonstrated higher rates of revascularisation in patients treated with DCB
3) These favourable safety findings were also observed in exploratory analyses of ACS populations

Where drug eluting stents are the main guideline advised treatment for de novo coronary disease, there is an increasing body of evidence supporting that DCBs provide similar outcomes to DES from 12 to 60 months follow-up. However, when analysing revascularisation excluding small vessel only studies, there was a significant increase in revascularisation with DCB-only PCI.

The role of DCB angioplasty in de novo coronary disease has evolved substantially over the past decade. Early randomised studies were largely confined to small-vessel disease,[3,20,23] where the limitations of stent implantation are particularly relevant. This is driven partially by stent struts occupying a proportionally greater fraction of the artery lumen, resulting in a higher metal-to-artery ratio.[30] Whilst these studies consistently demonstrated favourable angiographic and clinical outcomes, it remained uncertain whether these findings could be extrapolated beyond the small-vessel setting, particularly to studies enrolling broader de novo coronary populations that included larger vessels. The interest in DCB-only PCI extends beyond treatment of small vessel disease and reflects the wider appeal of a stentless strategy. By avoiding permanent metallic implants, DCB angioplasty may preserve vessel physiology, reduce chronic inflammatory stimulus, eliminate the risk of mechanical stent failure, facilitate future percutaneous or surgical revascularisation, and potentially permit shorter duration of dual antiplatelet therapy in selected patients.[31] Larger coronary arteries are associated with different procedural challenges, lower baseline restenosis rates,[32] and historically, less evidence supporting a DCB-only approach. Consequently, uncertainty remained regarding both the efficacy and safety of DCB-only angioplasty outside the small-vessel setting. This uncertainty was heightened following the publication of the REC-CAGEFREE I trial,[22,30] where non-inferiority was not met due to higher rates of target vessel revascularisation in the DCB arm. More recently, the SELUTION De Novo trial[28] demonstrated non-inferiority of a sirolimus-eluting balloon compared with contemporary DES implantation. The present meta-analysis incorporates both of these landmark trials.

The findings of REC-CAGEFREE I,[21] where the Swide (paclitaxel) DCB failed to meet non-inferiority criteria compared to contemporary DES appear to differ from those observed with the other included studies. By contrast, SELUTION De Novo[28] demonstrated non-inferiority to contemporary DES, suggesting that there may be a role for DCB-only PCI in a more broadly applied inclusion criteria of any vessel size. REC-CAGEFREE I and SELUTION De Novo have quite considerably different study designs. REC-CAGEFREE I was a device trial in that randomisation occurred after pre-dilatation and lesion preparation, whereas SELUTION De Novo was a strategy trial, where randomisation occurred prior to lesion preparation. These

differences are particularly relevant in DCB angioplasty, where procedural success is heavily dependent on lesion preparation and appropriate bailout stenting. As a result, the two trials may not be addressing precisely the same clinical question, despite both comparing a DCB with DES approach. However, differences in follow-up duration is also important. Trial design alone is unlikely to fully explain the observed findings. SELUTION is currently reporting 1-year outcomes whilst REC-CAGEFREE I has reported 3-year outcomes. Ongoing follow-up of SELUTION De Novo will therefore be important to determine whether the favourable outcomes remain over time.

Interpretation of the SELUTION De Novo also requires some caution. Although the trial met its prespecified non-inferiority margin on intention-to-treat analysis, aspects of the non-inferiority margin have been debated, and the secondary per-protocol analysis failed to meet non-inferiority. This discrepancy may reflect differences in the analysed populations after protocol deviations and crossover due to need for bailout stenting, together with the smaller effective sample size of the per-protocol cohort, rather than true conflicting treatment effect differences. Longer-term follow-up of SELUTION De Novo, together with the results of subsequent randomised trials, will help determine whether these observations persist over time. Nevertheless, the findings of this meta-analysis remained consistent even with leave-one-out sensitivity analyses excluding SELUTION De Novo, suggesting that the overall conclusions are not dependent on the inclusion of this trial.

It is important to consider the lack of class effect that applies across all DCB technologies. Whilst the majority of DCBs in this meta-analysis are paclitaxel coated balloons, the pharmacokinetic properties, coating technologies and supporting clinical evidence differ between devices. Early data regarding tissue absorption and drug transfer-kinetics of the Swide balloon have not been widely published, and the device is not commercially available outside the REC-CAGEFREE programme. Furthermore, the clinical evidence supporting the Swide DCB prior to REC-CAGEFREE I was limited to a single analysis comparing this balloon to another in in-stent restenosis patients looking at angiographic late lumen loss at 9-months.[33] Consequently, differences in device characteristics may represent one potential explanation for the variation in findings observed between REC-CAGEFREE I and other contemporary DCB trials, although this hypothesis remains speculative. More broadly, comparative data between sirolimus and paclitaxel-coated balloons remains limited. Although early comparative studies suggest broadly similar clinical outcomes,[34] differences in coating technology, drug transfer kinetics and excipients mean that equivalence between DCB platforms cannot currently be assumed.

An important strength of this meta-analysis is the inclusion of both small-vessel trials and six contemporary trials enrolling broader de novo coronary populations, allowing assessment of treatment effects across a wider spectrum of lesion subsets (6365 patients from any vessel size). The large vessel (>3 mm) subgroup analysis of REC-CAGEFREE I suggested a significant increase in the primary composite endpoint in this group not substantiated by our work given the findings of the sensitivity analysis excluding small vessel-only studies. There had been a signal to numerical increase in cardiovascular death in the REC-CAGEFREE I trial which has not been corroborated by this analysis.

The findings relating to revascularisation outcomes warrant careful consideration. Whilst there were no significant differences in revascularisation across all studies, exclusion of small-vessel-only trials resulted in significantly higher rates of TLR/TVR in the DCB arm. Importantly, these findings were strongly influenced by REC-CAGEFREE I. Revasularisation endpoints should also be interpreted cautiously as it is recognised that the relevance of revascularization as an outcome is limited by the fact that repeat procedures are subject to variability in clinical judgement, patient preference, and local practice.[35] Although revascularisation endpoints varied across trials, importantly, the findings were unchanged when the analysis was restricted to studies reporting TLR, suggesting that the results were not driven by difference in revascularisation endpoint definitions. To further explore the influence of vessel size, additional subgroup analyses stratified according to studies restricted to small-vessel disease and studies enrolling non-small-vessel populations did not demonstrate significant effect modification for cardiovascular death, myocardial infarction or revascularisation outcomes. Although numerically higher revascularisation rates were observed in non-small-vessel studies, formal interaction testing was not significant. These findings suggest that the observed differences are unlikely to be explained by vessel size alone and may instead reflect the broader heterogeneity between studies, including differences in clinical presentation, lesion complexity, DCB technology, endpoint definitions and follow-up duration.

Despite this heterogeneity, the findings of cardiovascular death, myocardial infarction and lesion thrombosis remained consistent across multiple sensitivity analyses, supporting the robustness of the safety findings. Importantly, the findings relate to a DCB-based strategy rather than pure DCB-only angioplasty, as bailout stenting was permissible in the included studies.

Several contemporary all-comer RCTs, including TRANSFORM II trial NCT04893291, CAGE-FREE III NCT05209412, The Reverse trial NCT05846893 are currently underway and will further define the role of DCB-only PCI across a broad spectrum of de novo coronary disease. This meta-analysis adds strength to

the role of DCB-only PCI in any vessel size. An exploratory analysis of ACS populations also demonstrated no significant difference in MACE between treatment strategies. However, interpretation is limited by heterogeneity in endpoint definitions and the lack of individual endpoint reporting in some subgroup analyses. Interpretation of the non-small-vessel analysis requires caution, as studies not restricted to small vessels also differed with respect to clinical presentation, with several enrolling ACS populations exclusively. Consequently, differences observed in revascularisation outcomes may reflect a combination of vessel size, clinical presentation, device characteristics, and trial design rather than vessel size alone.

This meta-analysis has several important limitations. Firstly, the meta-analysis was performed using aggregate trial-level data rather than individual patient-level data, limiting adjustment for differences in baseline characteristics and preventing complete synthesis of endpoints across trials. To mitigate this, we have instead conducted an analysis based on the individual components of the endpoints given the substantial variation in MACE definitions between trials. Secondly, there was considerable clinical and methodological heterogeneity across the included studies. Patient populations varied with respect to clinical presentation, including stable coronary disease and acute coronary syndromes, and lesion subsets ranged from small-vessel disease to all-comer de novo disease. Thirdly, important differences existed between DCB technologies. Although most studies evaluated paclitaxel-coated balloons, important differences exist between DCB technologies and a class effect cannot be assumed.

Furthermore, there was heterogeneity in study design, including differences in randomisation strategy, lesion preparation protocols, bailout stenting thresholds and comparator DES platforms. Follow-up duration ranged from 12 to 60 months, which may have influenced event ascertainment and limited direct comparability between studies. In addition, several outcomes were influenced predominantly by the largest contemporary trials. However, leave-one-out sensitivity analyses demonstrated that the overall findings were generally robust to exclusion of individual studies. Revascularisation endpoints should also be interpreted in the context of differing follow-up strategies, as protocol-mandated angiographic surveillance in some studies may have increased rates of repeat revascularisation through identification of asymptomatic restenosis. Assessment of publication bias was limited by the relatively small number of included studies. Finally, the results may not be generalisable to more complex lesion subsets, including left main stem disease and chronic total occlusions, which were excluded from the included randomised trials.

There are comparable event rates between DCB and DES-only PCI for de novo coronary disease for cardiovascular death, myocardial infarction and treated lesion thrombosis, a finding which remains true when excluding small vessel only trials with 7832 patients and 10 RCTs comparing DCB to 2nd generation or newer DES at twelve to sixty-month follow-up. This may support the safe use of DCB across any vessel size within the studied lesion subsets and across all clinical presentations. Whilst there was no difference in TLR across all studies, the higher rates of target lesion revascularisation when excluding small vessel-only trials support the continued evaluation of DCB-only PCI in selected de novo coronary artery lesions but should be interpreted in the context of important heterogeneity between DCB technologies and trial design.

Contributors

Conceptualisation: NC, RN, VV, and SCE; data curation: NC, RN, IM, and VT; formal analysis: NC, AC; investigation: NC; methodology: NC, VT, and VV; project administration: NC; resources: AC, VV; supervision: AC, SCE, and VV; writing- original draft: NC; writing-reviewing and editing: NC, RN, IM, VT, AC, SCE, VV. NC, and RN accessed and verified the underlying data.

Data sharing statement

All data used in this manuscript can be found in the online versions of studies that were accessed. Our own data synthesis is available upon reasonable request to the corresponding author after publication. Access to the data will require a signed data sharing form.

Declaration of interests

NC was funded by an NIHR Doctoral Research Fellowship (NIHR303008). VT received an NIHR Doctoral Research Fellowship grant (NIHR303306), independent of this work. VV reports speaker fees from Novartis and Daichii-Sankyo and received a grant for investigator-initiated research by B Braun, independent of this work. SCE received speaker fees and acts as a consultant for B Braun, Medtronic, Cordis and MedAlliance, and received grants for investigator-initiated research from B Braun, independent of this work. IM received a grant for investigator-initiated research by Cordis, independent of this work. All other authors declare no competing interests.

Acknowledgements

For the purpose of open access, the authors have applied a Creative Commons Attribution Licence (CC BY) to any author accepted manuscript version arising from this submission. NC and VT are supported by National Institute of Health and Care Research (NIHR) Doctoral Research Fellowship grants (NIHR303008 and NIHR303306 respectively).

AI has not been used in the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.104204.

References

1 Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45:3415–3537.

2 Collet J-P, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289–1367.

3 Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel 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;60:2473–2480.

4 Latib A, Ruparelia N, Menozzi A, et al. 3-Year Follow-Up of the balloon elution and late loss optimization study (BELLO). *JACC Cardiovasc Interv*. 2015;8:1132–1134.
5 Jeger RV, Farah A, Ohlow M-A, 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;396:1504–1510.
6 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;16:1054–1061.
7 Liu S, Zhou Y, Shen Z, et al. Comparison of drug-coated balloon and drug-eluting stent for the treatment of small vessel disease (from the dissolve SVD randomized trial). *Am J Cardiol*. 2024;211:29–39.
8 Tang Y, Qiao S, Su X, et al. Drug-coated balloon versus drug-eluting stent for small-vessel disease: the RESTORE SVD China randomized trial. *JACC Cardiovasc Interv*. 2018;11:2381–2392.
9 Fezzi S, Giacoppo D, Fahrni G, et al. Individual patient data meta-analysis of paclitaxel-coated balloons vs. drug-eluting stents for small-vessel coronary artery disease: the ANDROMEDA study. *Eur Heart J*. 2025;46:1586–1599.
10 Corballis N, Merinopoulos I, Bhalraam U, et al. Comparison of drug coated balloon with drug eluting stent for isolated ostial side-branch coronary artery bifurcation lesions. *Am J Cardiol*. 2026;258:257–260. published online Oct 14. https://doi.org/10.1016/j.amjcard.2025.09.059.
11 Merinopoulos I, Corballis N, Gunawardena T, et al. Assessment of scoring balloons in STEMI patients treated with DCB-only angioplasty: a single center study. *Health Sci Rep*. 2025;8:e70839. https://doi.org/10.1002/hsr2.70839.
12 Shin ES, Jun EJ, Kim S, et al. Clinical impact of drug-coated balloon–based percutaneous coronary intervention in patients with multivessel coronary artery disease. *Cardiovasc Interv*. 2023;16:292–299. https://doi.org/10.1016/J.JCIN.2022.10.049.
13 Kim S, Lee J-S, Kim Y-H, et al. Favorable vasomotor function after drug-coated balloon-only angioplasty of de novo native coronary artery lesions. *J Clin Med*. 2022;11:299. https://doi.org/10.3390/jcm11020299.
14 Covidence - better systematic review management. https://www.covidence.org/. Accessed October 26, 2025.
15 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
16 Schünemann H, Brożek J, Guyatt G, Oxman A. The GRADE handbook. https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/10284249; 2013. Accessed October 23, 2025.
17 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
18 Vos NS, Fagel ND, Amoroso G, et al. Paclitaxel-coated balloon angioplasty versus drug-eluting stent in acute myocardial infarction. *JACC Cardiovasc Interv*. 2019;12:1691–1699.
19 Niehe SR, Vos NS, Van Der Schaaf RJ, et al. Two-year clinical outcomes of the REVELATION study: sustained safety and feasibility of paclitaxel-coated balloon angioplasty versus drug-eluting stent in acute myocardial infarction. *J Invasive Cardiol*. 2022;34(1):39–42.
20 Cortese B, Di Palma G, Guimaraes MG, et al. Drug-coated balloon versus drug-eluting stent for small coronary vessel disease: PICCOLETO II randomized clinical trial. *JACC Cardiovasc Interv*. 2020;13:2840–2849.
21 Gao C, He X, Ouyang F, 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;404:1040–1050.
22 Naganuma T, Latib A, Sgueglia GA, et al. A 2-year follow-up of a randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels the BELLO study. *Int J Cardiol*. 2015;184:17–21.
23 Jeger RV, Farah A, Ohlow M-A, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018;392:849–856.
24 Wang Z, Yin Y, Li J, et al. New ultrasound-controlled paclitaxel releasing balloon vs. asymmetric drug-eluting stent in primary ST-Segment elevation myocardial infarction - a prospective randomized trial. *Circ J*. 2022;86:642–650.
25 Hao X, Huang D, Wang Z, Zhang J, Liu H, Lu Y. Study on the safety and effectiveness of drug-coated balloons in patients with acute myocardial infarction. *J Cardiothorac Surg*. 2021;16:178.
26 Yu X, Wang X, Ji F, et al. A non-inferiority, randomized clinical trial comparing paclitaxel-coated balloon versus new-generation drug-eluting stents on angiographic outcomes for coronary de novo lesions. *Cardiovasc Drugs Ther*. 2022;36:655–664.
27 Mangner N, Farah A, Ohlow M-A, et al. Safety and efficacy of drug-coated balloons versus drug-eluting stents in acute coronary syndromes: a prespecified analysis of BASKET-SMALL 2. *Circ Cardiovasc Interv*. 2022;15:e011325.
28 Spaulding C, Krackhardt F, Bogaerts K, et al. Sirolimus-eluting balloon with provisional stenting versus systematic drug-eluting stent implantation to treat de novo coronary lesions: a randomized, open-label, noninferiority trial. *Circulation*. 2026;154:185–197. published online June 15. https://doi.org/10.1161/CIRCULATIONAHA.126.079033.
29 Ling Tao MP, Xingqiang He M, Guidong Shen MP, et al. Drug-coated balloon angioplasty versus upfront stenting for de novo CAD: 3-year follow-up of REC-CAGEFREE I trial. *J Am Coll Cardiol*. 2025. https://doi.org/10.1016/J.JACC.2025.10.027.
30 Briguori C, Sarais C, Pagnotta P, et al. In-stent restenosis in small coronary arteries. *J Am Coll Cardiol*. 2002;40:403–409.
31 Colombo A, Leone PP, Ploumen EH, von Birgelen C. Drug-coated balloons as a first choice for patients with de novo lesions: pros and cons. *EuroIntervention*. 2024;20:e120–e122.
32 Elezi S, Kastrati A, Neumann F-J, Hadamitzky M, Dirschinger J, Schömig A. Vessel size and long-term outcome after coronary stent placement. *Circulation*. 1998;98:1875–1880.
33 Zhu J, Liu L, Zhu Z, et al. A randomized comparison of a novel iopromide-based paclitaxel-coated balloon Shenqi versus SeQuent please for the treatment of in-stent restenosis. *Coron Artery Dis*. 2021;32:526–533.
34 Leone PP, Calamita G, Gitto M, et al. Sirolimus- versus paclitaxel-coated balloons for treatment of coronary artery disease. *Am J Cardiol*. 2025;255:74–82.
35 Lamelas P, Belardi J, Whitlock R, Stone GW. Limitations of repeat revascularization as an outcome measure: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:3164–3173. published online Dec 24. https://doi.org/10.1016/J.JACC.2019.10.041.