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Drug coated balloon angioplasty for de novo coronary lesions in large vessels: a systematic review and meta-analysis

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We aimed to investigate the safety of drug-coated balloon (DCB)-only percutaneous coronary intervention compared to drug-eluting stent (DES) for de novo lesions in large vessels. To pursue this goal, we conducted a systematic review and meta-analysis following the PRISMA guidelines. The analysis included studies that utilized DCB-only or hybrid angioplasty for de novo lesions in large coronary vessel (> 2.75 mm). The primary outcome was to assess the target lesion revascularization (TLR) rate, while secondary outcomes included cardiac death, myocardial infarction (MI), and the composite of these. A total of 15 studies, comprising 3975 patients (of whom 2114 treated with DCB) were included. Median age was 62 ± 1.5 years, with 77.4% being male. Overall, 26.9% had diabetes, and 67.6% were diagnosed with acute coronary syndrome. Over a pooled follow-up of 20.6 ± 1.9 months, the incidence of TLR was 4% in the pooled DBC group. Additionally, over a pooled follow-up of 25.8 ± 2.7 months, no significant differences were observed in incidence of TLR between the DCB group and the DES group (4.3% vs. 6.9%, odds ratio 0.71, 95% confidence interval 0.50–1.01, $p = 0.059$). Furthermore, there were no differences in incidence of cardiac death and MI. DCB angioplasty treatment of de novo lesions in large coronary vessels could be a safe and effective strategy in both acute and chronic coronary settings. The incidence of target lesion revascularization appears to be similar to that of contemporary DES.

Keywords Drug-coated balloon, Drug-eluting stent, Acute coronary syndrome, Target lesion revascularization

Percutaneous coronary intervention (PCI) has evolved significantly over the past decades. The introduction of coronary stenting helped overcome main limitations of plain old balloon angioplasty, as flow-limiting dissections and elastic recoil. Subsequently, in-stent restenosis (ISR) rates due to exaggerated neointimal growth in bare-metal stents (BMS) were soon recognized, facilitating the development of drug-eluting stents (DES). However, although second generation DESs have markedly improved PCI outcomes, the ongoing risk of very-late stents events occurs in approximately 2% of patients per year, with no evident plateau, even though 5-year follow-up. Consequently, these events still pose a challenge[1,2]. Recently, drug-eluting balloons (DCB) have emerged as an alternative therapeutic option for ISR of BMS or DES and for de novo lesions located in small coronary vessels[3]. This technology allows the homogenous delivery of high concentrations of antiproliferative drug using a semi-compliant balloon, without leaving metal or polymer behind, which is associated with chronic inflammation, the trigger for late thrombosis and ISR[4].

Previous randomized controlled trials (RCTs) have reported that DCB exhibit similar long-term clinical outcomes to DES, confirming their promising role in treatment of de novo lesion in small vessels[5–8]. Recently, the use of DCB-only treatment of de novo lesions in large vessels have garnered considerable attention, although

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it remains a subject of controversy. In order to reduce the total length of DES implanted and to shorten the duration of dual antiplatelet therapy (DAPT), this strategy could be of great value, especially in the context of long and multivessel coronary artery disease, in patients at high bleeding risk (HBR) patients, and in those who are candidate to surgery[9–13]. Against this backdrop, the primary endpoint of the present meta-analysis is to provide a comprehensive and quantitative assessment of the safety and efficacy of DCB in *de novo* coronary lesions in large vessels. Additionally, we aim to compare the incidence of safety and efficacy outcomes in patients treated with DCB compared to DES in large vessels.

Methods

The present study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[14]. The systematic review was registered on PROSPERO with the following identifier: CRD42024514519. The PubMed, OVID, Scopus, google Scholar and Cochrane library databases, were interrogated from inception to 30th November 2023, selecting all English-language articles that investigated the roles of DCBs for the treatment of de novo coronary lesions in large vessels. Studies were identified by using search terms, MeSH terms and keywords and crossing the following terms: "drug coated balloon", "drug eluting balloon", "coronary artery disease", "de novo lesion", "large vessel". Three reviewers (C.G., F.G. and G.P.) independently reviewed the databases. References from relevant studies were screened for supplementary articles. We included retrospective and prospective registries, retrospective case-control studies with and without propensity-scoring matched groups, and clinical randomized trials comparing DCB and DES for the treatment of de novo lesions in large vessels. We chose the cut-off of 2.75 mm to identify large coronary arteries[5,7].

Main inclusion criteria were: (1) de novo lesions treated with DCB, (2) reference diameter of the target vessel > 2.75 mm or mean reference diameter > 3 mm with a standard deviation (SD) ± 0.25 mm.

In most studies, the reference lumen diameter was estimated visually through angiography. Both chronic and acute clinical presentations were considered, including ST-elevation myocardial infarction (STEMI).

We considered the target lesion revascularization (TLR) as the primary outcome, as it was reported in all included studies; conversely, secondary outcomes were myocardial infarction (MI), cardiac death (CD) and a composite endpoint, called target lesion failure (TLF). It is worth noting that the composite endpoint was not consistently defined across all studies or was sometimes unavailable. In most studies, TLF was defined as a combination of CD, MI, and TLR. Additionally, in three studies, (Nakamura et al., Li et al., Gitto et al.) the composite endpoint included target vessel revascularization (TVR) alongside the aforementioned endpoints".

Data extraction

Two independent investigators (F.G. and G.P.) reviewed all search results and selected the studies in accordance with inclusion criteria. When a consensus was not reached, a third reviewer was consulted for final decision (C.G). For each eligible study, we extracted data including article information (first author and year of publication), study characteristics, relevant population demographics and angiographic and procedural details. In one case we asked the corresponding author for supplementary data regarding outcomes[15], and in another case we asked for a *sub-analysis* of patients with a reference vessel diameter > 2.75 mm[16]. Since all analyses were based on previous published studies, there is no requirements for ethical approval or patient consent. The investigation is in line with the principles of the Declaration of Helsinki.

Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Statistical analysis

To calculate the pooled incidence rate of TLR, CD, MI and TLF in the populations treated with DCB, we performed a meta-analysis using the Comprehensive Meta-Analysis Version 2 (Biostat, Englewood, NJ) of data from all studies published. We also conducted a meta-analysis of principal baseline and angiographic characteristics of patients treated with DCB from all studies. Pooled demographic and clinical data derived from the analysis were expressed mean with standard error (SE) or event rate with confidence intervals (CI).

Additionally, we calculated the pooled incidence of outcomes of DCB and DES-treated groups from controlled studies, and we compared them. In this case, results of the comparison were expressed as odds ratios (ORs) with 95% CI. The limit of statistical significance was set at $P < 0.05$.

Heterogeneity was assessed using I-square, Q, and tau-square values. Random effect models were applied when heterogeneity across studies was high ($I^2 > 75$) and fixed models when the heterogeneity was lower ($I^2 < 75$). Publication bias was assessed by using the funnel plot method (Trim and fill test). To assess and adjust for publication bias, this method involves estimating the number of missing studies (those that would have filled the funnel plot) and imputing them to create a more symmetrical funnel plot, thereby providing a more accurate estimate of the overall effect size[17]. Observed and adjusted values, their lower and upper limits have been calculated. To assess the effect of individual studies on the pooled result, we conducted a sensitivity analysis by excluding each study one by one and recalculating the combined estimates on remaining studies. The sensitivity analysis ruled out the presence of a single study effect, and no significant publication bias was detected.

Results

The PRISMA flowchart, illustrating the search strategy and manuscript selection process, is presented in Supplementary Fig. 1. After removing duplicates, the initial literature search yielded a total of 45 papers. Among them, 12 were excluded because they also included PCI in small coronary vessels. Additionally, 6 papers were

excluded due to unavailable data on reference vessel diameter, 8 were case reports or case series, and 4 were reviews, commentaries or editorials. Finally, 15 studies met the inclusion criteria and were included in the present meta-analysis. Of the 15 studies, 8 were retrospective case-control studies, 1 was prospective randomized trial, and 6 uncontrolled registries. The total number of patients included across these studies was 3975. Specifically, 2114 patients were treated with DCB across 15 studies. In the 9 controlled studies, 1356 patients received DCB treatment, and 1861 patients were treated with DES, resulting in a total of 3217 patients.

The complete list of the included studies is provided in Tables 1 and 2. Notably, 4 studies excluded patients with acute myocardial infarction (AMI)[9,16,18,19], while 2 studies focused exclusively on patients with STEMI undergoing primary PCI[15,24]. Patients with unstable clinical presentation (such as cardiogenic shock, cardiac arrest, or requiring intubation) were excluded from all studies. Additionally, 4 studies excluded patients with severe left ventricular dysfunction (defined as left ventricular ejection fraction < 35%) or end-stage chronic kidney disease (estimated glomerular filtration rate, eGFR < 30 ml/min*m^2)[9,19,25,26]. Two studies enrolled patients with lesions only in the left anterior descending artery (LAD)[25,28], while another study focused on patients with lesions in left main vessel[29]. In all included studies, lesion preparation followed the drug coated balloon consensus document, including predilatation with non-compliant or cutting balloons, as well as calcium modifiers (intracoronary lithotripsy or rotational atherectomy)[30]. After lesion preparation, bailout stenting was performed in cases of residual flow-limiting dissection or significant residual stenosis. While all studies provided clinical follow-up, two studies also included angiographic planned follow-up[18,25].

Baseline clinical and angiographic characteristics of patients treated with DCB

Clinical and angiographic characteristics are reported in Tables 1 and 2. Regarding the 2114 patients treated with DCB-based PCI, the majority were male (77.4%, data from 14 studies, $n = 1716$) with a mean age of 62.1 ± 1.5 years (data from 14 studies, $n = 1716$), as shown in Tables 1 and 2. Among them, 358 (26.9%) were diagnosed with diabetes (14 studies, $n = 1716$). Many studies focused on patients with acute coronary syndrome (67.6%, 13 studies, $n = 1926$), and the majority of treated were located in the LAD (59%, 14 studies, $n = 1716$). Most studies used DCB coated with Paclitaxel (98%, 13 studies, $n = 1680$). The mean reference diameter of the target vessel was 3.24 ± 0.01 mm (14 studies, $n = 1716$), and the mean lesion length of 24.44 ± 2.04 mm (11 studies, $n = 1547$). The PCI involved a bifurcation in 53.7% of cases (9 studies, $n = 1151$), and 39.4% of patients presented with multivessel coronary artery disease (9 studies, $n = 1143$). In 8.2% of cases (9 studies, $n = 1264$), bailout stenting

References	Sample size	Country/inception date	Study design	Age	Male (%)	Diabetes (%)	STEMI (%)	NSTEMI (%)	Stable angina (%)
Vos et al., 2019[24]	60	Holland 2014–2017	Prospective trial DCB vs DES in STEMI patients	57.4 ± 9.2	87	13	100	0	0
Li et al., 2022 [25]	49	China 2017–2019	Retrospective case–control, DCB-only vs DES strategy in ostial lesions in the left anterior descending artery	61.2 ± 10.7	76	24	n.a.	n.a.	n.a.
Liu et al., 2022 [9]	36	China 2018–2019	Retrospective case–control, DCB-only vs DES in the treatment of de novo left main coronary artery bifurcation lesions	57.8 ± 11.4	80.6	27	0	77.8	22.2
Merinopoulos et al., 2023[16]	398	UK 2015–2019	Retrospective case–control DCB-only vs DES for first presentation of stable angina	n.a.	n.a.	n.a.	0	0	100
Gitto et al., 2023[28]	139	Italy 2018–2022	Retrospective case–control, left anterior descending PCI DES vs DCB-only PCI and those receiving hybrid PCI	69.3 ± 10.22	84.4	31	n.a.	n.a.	n.a.
Gunawardena et al, 2023.[29]	41	UK 2014–2019	Retrospective case–control; DCB vs II-generation DES for de novo unprotected LMS disease	73.8 ± 11.7	85.4	31	12.2	56.1	31.7
Merinopoulos et al, 2023.[15]	452	UK 2016–2019	Retrospective case–control, DCB-only vs II-generation DES only for first presentation of STEMI	66 ± 13	73	14	100	0	0
Nakamura et al., 2023[18]	73	Japan 2016–2018	Retrospective case–control, DCB vs DES in electively patients	67.1 ± 11.4	84.9	49	0	0	100
Pan et al., 2023 [19]	108	China 2015–2019	Retrospective case–control, DCB-only or hybrid strategies in de novo ostial lesions in the LAD or LCx	58.8 ± 10.3	71.3	34	0	61.1	38.9
Yu et al.,2019[20]	200	China 2014–2017	Retrospective registry, large vessel disease group (RD) ≥ 2.8 mm vs small vessel disease group DCB-only PCI	61.7 ± 11.3	74.5	27	2	89.5	8.5
Liu et al., 2019[21]	120	China 2016–2017	Prospective registry, feasibility, safety, and efficacy of DCB only PCI in vessels exceeding 3.0 mm	57.6 ± 11.3	78	30	9.1	78.3	12.5
Lu et al., 2019[22]	92	China	Prospective registry, DCB in de novo lesions in large coronary artery	52.3 ± 10.7	78.3	19	5.4	45.7	48.9
Rosenberg et al., 2019[23]	134	Europe/Malaysia	Retrospective registry, efficacy of DCB as a stand-alone-therapy in de novo lesions	63.4 ± 11.8	88.1	35	11.9	50	38.1
Hu et al., 2022 [26]	119	China 2017–2020	Prospective registry, DCB-only strategy for the treatment of de novo bifurcation and non-bifurcation lesions	55.3 ± 10.8	72	24	13	78	8
Leone et al., 2023[27]	93	Italy 2020–2022	Retrospective registry, DCB angioplasty or hybrid for de novo lesions	68 ± 11	89	25	n.a.	17	83

Table 1. Study design and baseline characteristics in DCB treated patients. *DCB* drug coated balloon, *DES* drug eluting stent, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non-ST elevation myocardial infarction, *LMS* left main stem, *LAD* left anterior descending, *LCx* Left Circumflex artery. n.a., not available.

References	LAD (%)	LCx (%)	RCA (%)	Reference vessel diameter (mm)	Lesion length (mm)	Bifurcation (%)	Severe calcification (%)	Multivessel disease (%)	Paclitaxel eluting ballon (%)	Hybrid approach (%)	Bailout DES (%)
Vos et al., 2019 [24]	32	20	48	3.28 ± 0.52	n.a.	n.a.	0	26.7	100	n.a.	18
Li et al., 2022 [25]	100	0	0	3.36 ± 0.45	19.1 ± 5.7	100	2	41	100	n.a.	n.a.
Liu et al., 2022 [9]	86.1	47.2	0	3.48 ± 0.56	n.a.	100	0	100	n.a.	n.a.	n.a.
Merinopoulos et al. 2023[16]	n.r	n.r	n.r	n.r	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Gitto et al., 2023 [28]	100	0	0	3.12 ± 0.48	62.2 ± 31.4	30.9	n.a.	23.7	14.4	70.5	10.8
Gunawardena et al, 2023.[29]	100	0	0	3.84 ± 0.26	21.7 ± 7.8	73.2	4.8	n.a.	100	0	n.a.
Merinopoulos et al., 2023[15]	43	17	39	3.32 ± 0.37	25 ± 7.4	42	15	3.8	100	0	5.3
Nakamura et al., 2023[18]	34.2	23.3	39.7	2.98 ± 0.4	18.4 ± 4.3	15.1	6.8	49.3	100	n.a.	n.a.
Pan et al., 2023 [19]	73.1	26.8	0	3.43 ± 0.4	26.4 ± 14.3	100	7.41	n.a.	100	50.93	6.25
Yu et al., 2019[20]	45.5	22.5	30.2	3.24 ± 0.39	15.5 ± 5.7	n.a.	6.8	74	100	n.a.	0.5
Liu et al. 2019[21]	64.4	17	18.5	3.09 ± 0.31	17.5 ± 7.8	n.a.	7.4	n.a.	100	n.a.	1.6
Lu et al., 2019[22]	69.1	7.5	20.2	3.32 ± 0.46	12.3 ± 3.5	na.	0	n.a.	100	n.a.	6.4
Rosenberg et al., 2019[23]	42.9	26	26.6	3.15 ± 0.26	17.6 ± 8.3	16.9	21.4	35	100	8	n.a.
Hu et al., 2022 [26]	56.5	28.3	15.2	3.1 ± 0.3	14.2 ± 6.6	55.4	n.a.	n.a.	100	n.a.	n.a.
Leone et al. 2023[27]	48	25	28	3.2 ± 0.3	45 ± 26	n.a.	n.a.	n.a.	23	30	6

Table 2. Angiographic characteristics in DCB treated patients. *LAD* left anterior descending, *LCx* left circumflex artery, *RCA* right coronary artery, *DCB* drug coated balloon. n.a., not available.

was necessary after lesion preparation or following DCB implantation due to flow-limiting dissection or residual stenosis of the treated lesion.

Clinical outcomes in DCB-treated population

Considering the entire population of patients treated with DCB, at a mean follow up of 20.6 ± 1.9 months (data from 15 studies, $n = 2114$), the TLR, the primary outcome occurred in 4% of patients (95% CI 3.2–5.0%; 15 studies, $n = 2114$). As secondary endpoints, CD occurred in 3.5% of patients (95% CI 2.7–4.5%, 15 studies, $n = 2114$), MI in 5.7% (95% CI 4.5–7.0%, 15 studies, $n = 2114$), while TLF was observed in 5.3% of cases (95% CI 4.1–6.8, 12 studies, $n = 1223$; Supplemental Table 1).

Clinical outcomes in DCB versus DES group

In controlled studies comparing DCB and DES-treated patients (9 studies, 3217 subjects), the mean follow-up was 25.8 ± 2.7 months in the DCB-group (9 studies, $n = 1356$) and 26.8 ± 2.8 months in the DES group (9 studies, $n = 1861$). The mean age (63.9±1.8 vs. 64.8±1.5 years) and the proportion of patients presenting with ACS (61% vs. 58%) were comparable between the DCB and DES groups. Notably, there was a trend towards less TLR in DCB than DES (4.3% vs. 6.9%; OR 0.71, 95% CI 0.49–1.01, $p = 0.059$), although statistical significance was not reached (Fig. 1). MI occurred in 6.4% of patients treated with DCB vs. 5.9% with DES (OR 1.08, 95% CI 0.77–1.49, $p = 0.649$, 9 studies, $n = 3217$) (Fig. 2). CD occurred in 4.0% vs. 4.7% (OR 0.91, 95% CI 0.62–1.33, $I^2$19%, $p = 0.351$, 9 studies, $n = 3217$) (Fig. 3). Importantly, TLF occurred significantly less in DCB-treated group (6.1% vs. 16.0%, OR 0.37, 95% CI 0.22–0.59, $p < 0.001$, 6 studies, $n = 938$; Supplemental Tables 2 and in Fig. 4).

Discussion

To our knowledge, this is the largest comprehensive meta-analysis summarizing currently available data on feasibility, safety, and efficacy of DCB-only strategy for treating de novo lesions in large coronary vessels (reference diameter > 2.75 mm) at mid-term follow up.

This study, which included 3975 patients from 14 non-RCTs and 1 RCT, showed that in a pooled population of 2114 patients undergoing DCB-only PCI, at a mean follow-up of 20.6 ± 1.9 months, TLR occurred in 4%. Furthermore, over a pooled follow-up of 25.8 ± 2.7 months vs. 26.8 ± 2.8 months, DCB was associated with a trend toward a lower rate of TLR compared with patients treated with DES, although statistical significance was not reached. As secondary outcomes, no statistically significant difference in the incidence of CD and MI was found between the two groups, while the composite endpoint resulted significantly less frequent in DCB-treated patients.

At a mean follow up of 20.6 ± 1.9 months, the rate of TLR at 4% aligns with reported stent-related adverse events. Indeed, in a meta-analysis, Madhavan et al. postulated that among 13,380 patients treated with II generation DES, very-late ischemic events, occurred in approximately 2% of patients per year, with no plateau evident. During a follow-up period between 1- and 5-years, ischemia-driven TLR occurred in 4.4% of patients[1]. Moreover, our results revealed that compared to the recently available DES, DCB-only angioplasty for de novo lesions in large coronary arteries showed similar trends in terms of TLR (OR = 0.71, 95% CI 4.9 ± 1.01, I^2 56%, $p = 0.059$).

The trend toward a lower risk of TLR and the lower incidence of the composite endpoint in DCB group observed in our meta-analysis was mainly affected by the studies of Gitto et al.[28] and Pan et al.[19]. Gitto et al.

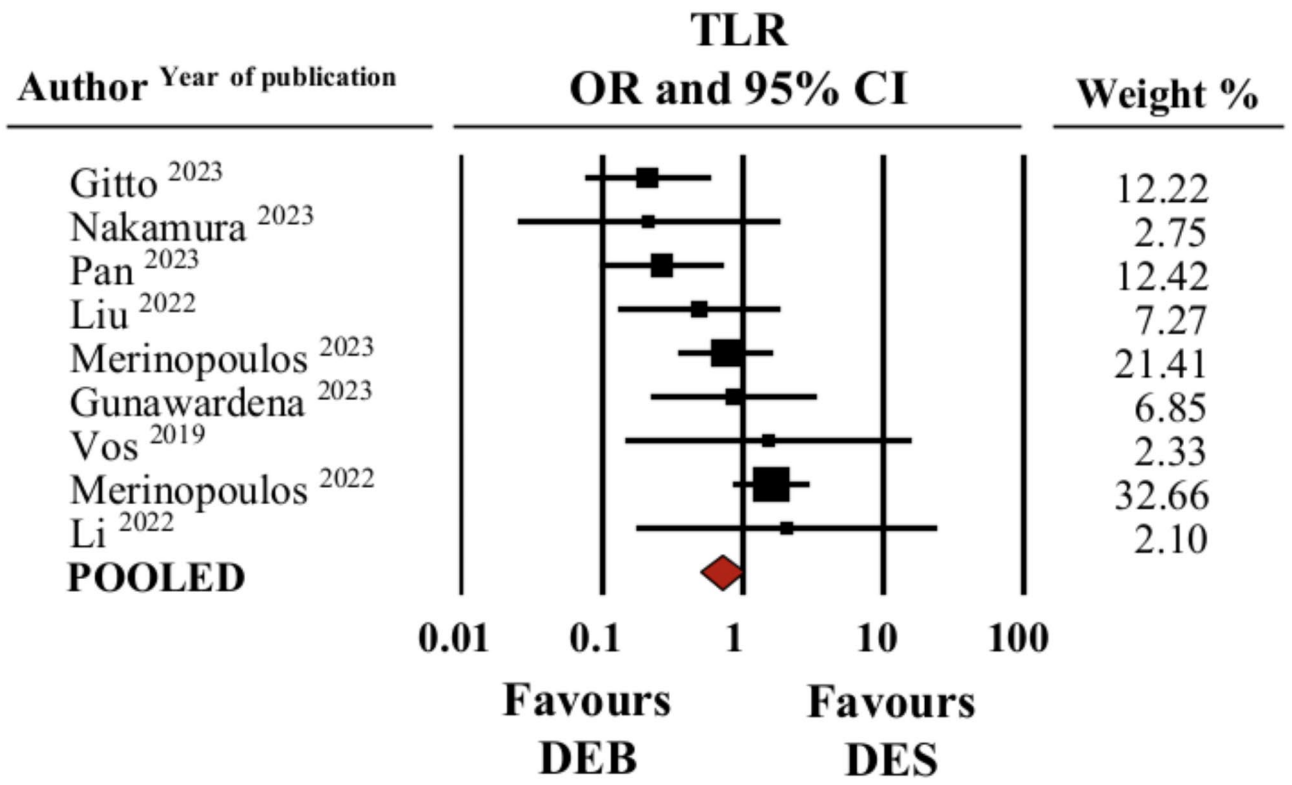

Fig. 1. Forest plot for target lesion revascularization (TLR) in DCB and DES treated patients. The red diamond indicates an OR of 0.71 (95% CI 0.49–1.01, $p = 0.059$).

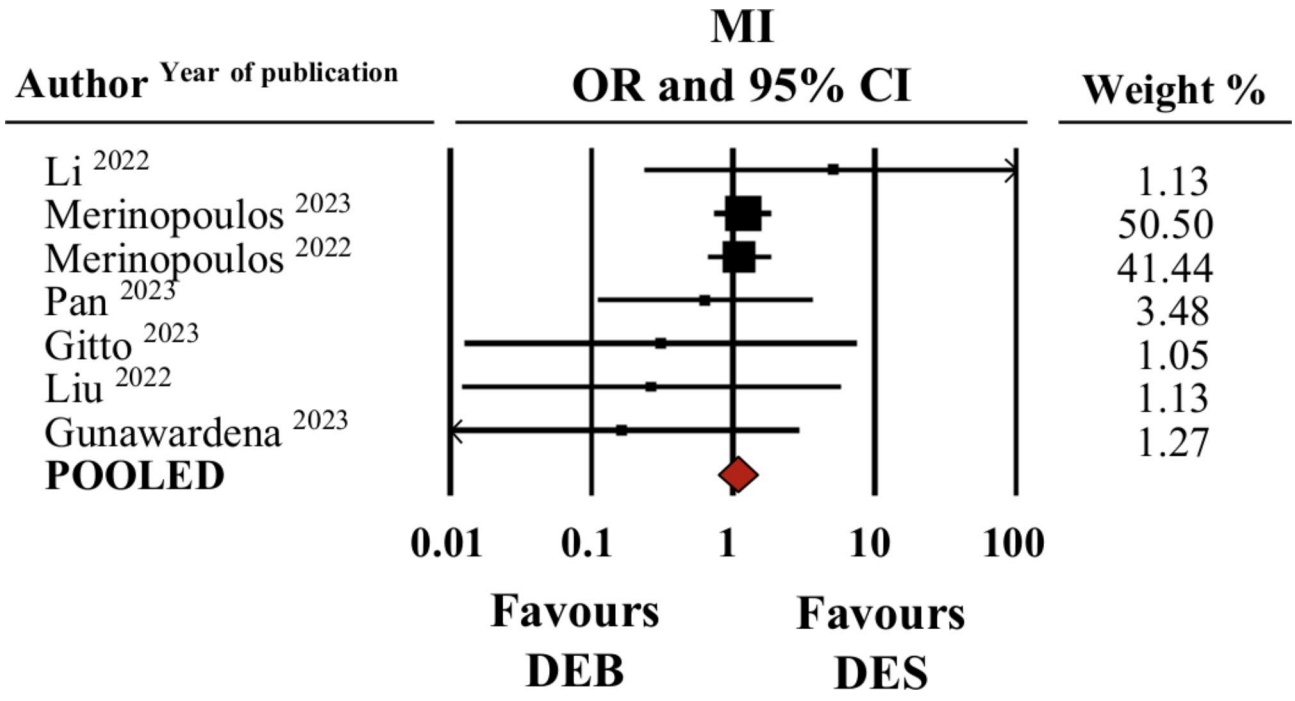

Fig. 2. Forest plot for myocardial infarction (MI) in DCB and DES treated patients. The red diamond indicates an OR of 1.08 (95% CI 0.77–1.49, $p = 0.649$). *DCB* drug coated balloon, *DES* drug eluting stent, *CI* confidence intervals, *OR* odds ratio.

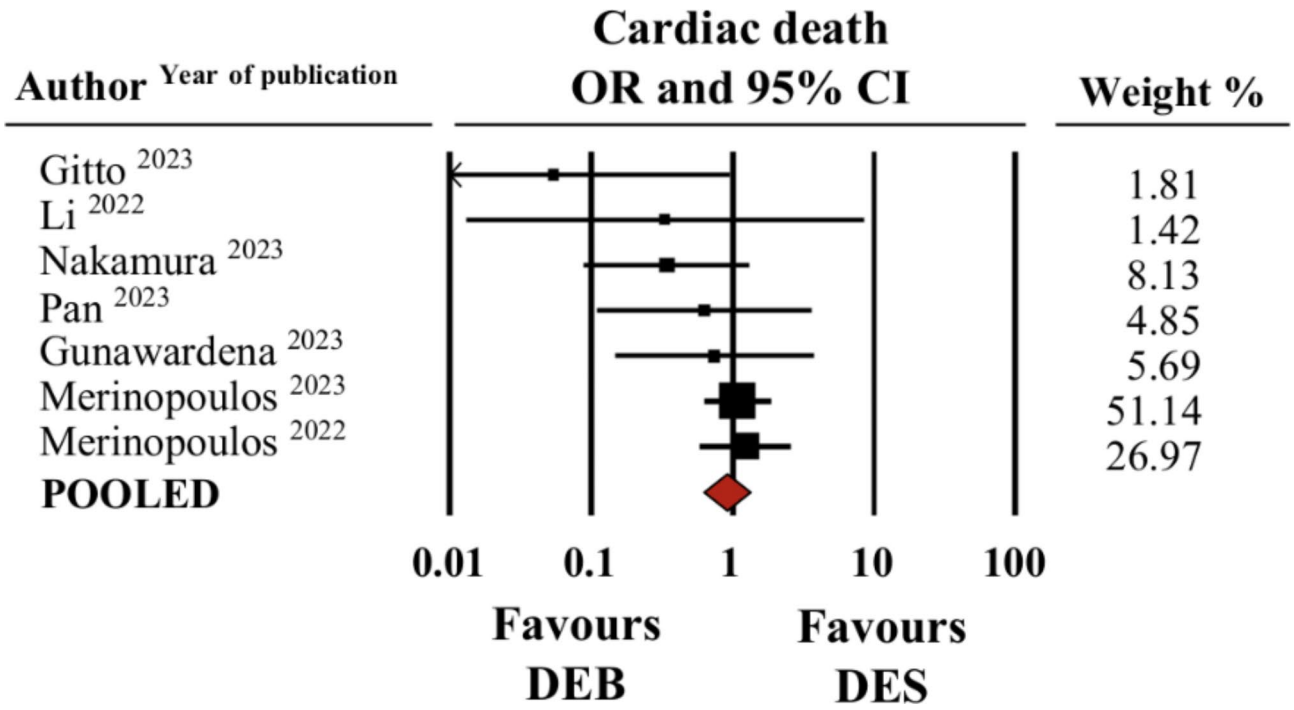

Fig. 3. Forest plot for cardiac death (CD) in DCB and DES treated patients. The red diamond indicates an OR of 0.91 (95% CI 0.62–1.33, $p = 0.351$). *DCB* drug coated balloon, *DES* drug eluting stent, *CI* confidence intervals, *OR* odds ratio.

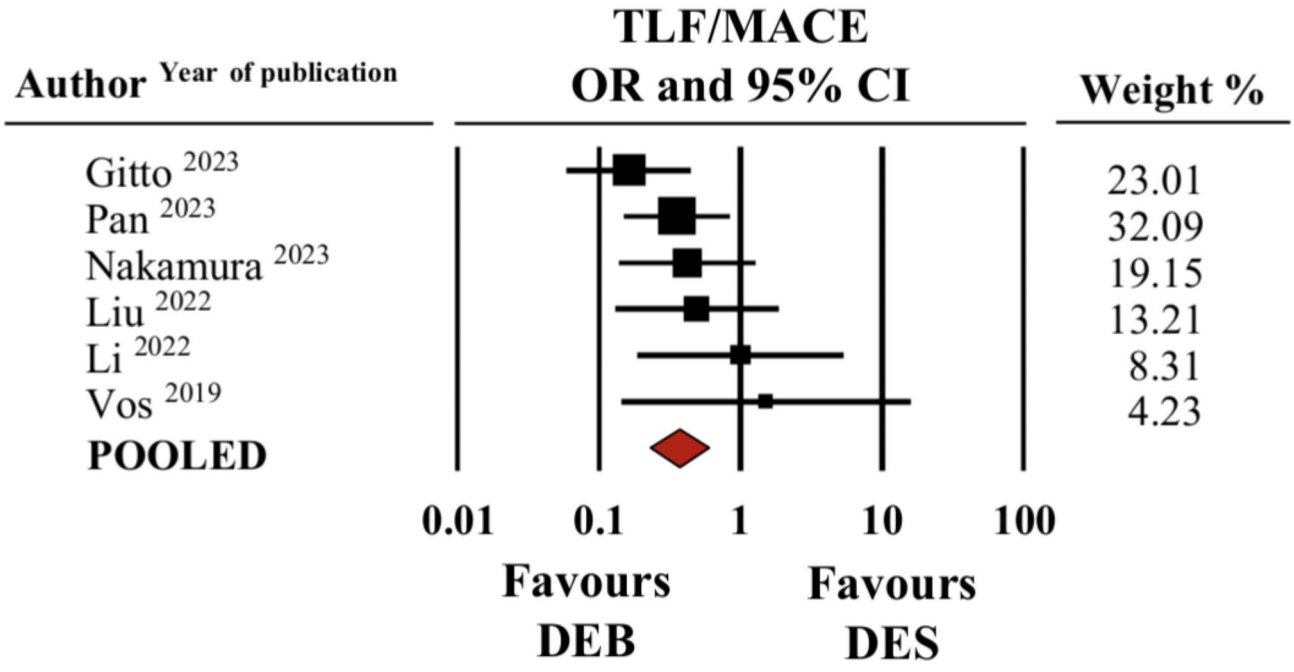

Fig. 4. Forest plot for target lesion failure (TLF) in DCB and DES treated patients. The red diamond indicates an OR of 0.37 (95% CI 0.22–0.59, $p < 0.001$). *DCB* drug coated balloon, *DES* drug eluting stent, *CI* confidence intervals, *OR* odds ratio.

reported a 2-year incidence of TLR and consequently of the composite TLF group significantly higher in DES group compared to DCB (14.6% vs. 3.5% and 18.2% vs. 3.5% respectively); the authors themselves state that the main reason behind these unusual findings were LAD lesion length (until 65 mm (40–82) mm in the DCB group vs. 56 (46–66) mm in the DES group). This may indicate a more significant effect of the use of DCB in the

context of diffuse atherosclerotic disease and long lesions, which are at a higher risk of ISR. Moreover, according to authors, the other reasons that may explain this finding is due to the repeated coronary angiographies for staged non-LAD revascularization, leading to an overestimation of non–clinically-driven TVR. Interestingly, they postulated the greater benefit in terms of TLR with longer follow-up. Most TLR occurred within the first 6 months in the DCB group, after which there was a plateau. In contrast, the DES showed a steadily growing TLR incidence in the DES group which is the natural history of stent-related negative vascular remodelling. However, it is essential to consider that the DCB population was treated with an hybrid approach in 70.8%, the highest rate among the studies included in the meta-analysis. This strategy was adopted at operator's discretion, taking into account the distal coronary-to-aortic pressure ratio post-lesion preparation[28].

In the study by Pan et al., after a propensity-matched sample, the authors reported an incidence of TLR of 4.9% in DCB group and 16.3% in the DES group. Additionally, the incidence of MACE (a composite of CD, target vessel MI and vessel thrombosis) of 7.8% in DCB group and 19.39% in the DES group. This discrepancy might be explained by the study's inclusion of only ostial LAD lesions (Medina classification 0,1,0). Ostial LAD lesions are traditionally considered a complex angioplasty, where optimal stent positioning is crucial to avoid acute and chronic complications. However, this limitation is overcome by balloon only angioplasty. Interestingly, the study revealed a significantly higher late lumen loss in DES group during follow-up compared to DCB group (0.30 ± 0.27 mm vs. -0.02 ± 0.57 mm, $p < 0.001$), effectively negating the advantage of the higher acute lumen gain observed after DES implantation (2.21 ± 0.52 mm vs. 1.63 ± 0.47 mm, $p < 0.001$). Possible explanations for this discrepancy include stent recoil or a negative remodeling including, which may involve neointimal hyperplasia or neoatherosclerosis[19].

"Leave nothing behind strategy"

Recently, a growing body of evidence has been published on the DES-limiting approach, which appears to be an encouraging strategy for overcoming stent-related adverse events mainly caused by the inflammatory reaction to stent and polymer. Plain-old balloon angioplasty (POBA) for coronary revascularization, was limited by acute elastic recoil and neointimal hyperplasia causing restenosis in about 30–40% of patients in the first 6 to 9 months. These limitations necessitated further technological advancement, leading in the introduction of coronary artery stents. However, despite contemporary DES markedly improving 1-year outcomes compared to BMS, the persistent occurrence of stent-derived adverse events, such as those described above, still poses a considerable cumulating risk. These DES limitations have spurred innovation for improved solutions, including the coronary vessel delivery of drugs via non-metallic-based platforms, such as DCB. Paclitaxel was identified as the primary drug for DCB due to its high lipophilic property and its ability to inhibit cell division and migration through irreversible binding to microtubules. This explains its long-lasting effects, lasting up to 12 days. In a recent meta-analysis by B. Scheller et al., including 26 RCTs published between 2006 and 2019, the use of paclitaxel DCB for treatment of coronary artery disease was associated with lower risk of death at longer-term follow-up when compared with non-DCB devices (such as conventional balloon angioplasty, bare-metal stents, or drug-eluting stents) in coronary intervention[31]. Despite the short exposure of the vessel wall, the bioavailability of paclitaxel is sufficient to achieve an arterial wall concentration high enough to reduce the process of restenosis. It is supposed that this phenomenon begins in the first days after the barotrauma induced by angioplasty[32].

From "leave nothing-" to "leave as little as possible-" behind strategy

The interest in this alternative strategy initially pertained the treatment of ISR and de novo lesions of small vessels. RCTs assessing the safety and efficacy of DCB-only strategy in de novo lesions of large vessels are lacking. Recently, the open-label, randomized, REC-CAGEFREE I trial did not achieve non-inferiority comparing a strategy of DCB angioplasty with rescue stenting with the intended DES implantation in de novo, non-complex coronary artery disease, in terms of the device-oriented composite endpoint (including CV, target vessel MI, and clinically and physiologically indicated TLR) assessed at 24 months. Of note, in a subgroup analysis of small- and non-small vessel disease (Reference Vessel Diameter < and > 3 mm, respectively), the authors found similar rates of DoCE between DCB and DES group in small vessel disease, while DES seemed to be more favorable in large vessel disease subpopulation (7.5% of DoCE in the DCB group vs. 2.5% in the DES group). Nevertheless, this subgroup analysis was not adjusted for multiple comparison and should be interpreted as explorative only. Notably, the Kaplan–Meier cumulative incidence curves of DoCE and its component endpoint between the DCB and DES groups began to diverge at approximately 100 days, favoring DES. This finding could be explained by the shorter local retention of the anti-proliferative drug which is typically 1 month for paclitaxel-coated balloons. Nevertheless, there is still limited randomized controlled trial (RCT) data focused on the safety and efficacy of DCB in large coronary artery disease. Of note, the "Drug-Coated Balloon versus Drug-Eluting Stent for Clinical Outcomes in Patients With Large Coronary Artery Disease (REVERSE)" a prospective, randomized, open-label, international multicenter trial is ongoing (ClinicalTrials.gov ID NCT05846893). The aim of study is to demonstrate the non-inferiority of drug-coated balloon (DCB) treatment compared to current-generation drug-eluting stenting (DES) in patients with large coronary artery disease (reference vessel diameter ≥ 3.0 mm by visual estimation) only[33]. Some other RCTs are ongoing and their results will be crucial to better evaluate the performance of DCBs in this clinical setting[34,35].

Moreover, this strategy, may be of great interest in treating anatomical settings such as bifurcations and long lesions. Current guidelines support the use of stenting of main branch (MB) with provisional stenting of the side branch as a default strategy, and in this setting, the use of DCB for side branch may be preferable to balloon angioplasty alone[36]. DCB-only strategy allows to reduce total stent length, which is one of the most important predisposing factors for ISR[37]. Furthermore, this strategy may also be of great interest in selected subsets, such as high-bleeding risk patients, where a 'leave nothing behind' strategy could offer a reduction of bleeding risk by means of a reduced duration of DAPT[12,13]. Lesion preparation is the cornerstone in the

DCB-only strategy. To ensure sufficient initial acute lumen gain, optimal pre-dilation is required, sometimes leading to severe dissection. Indeed, according to an international consensus on the use of DCBs, the presence of coronary artery flow-limiting dissection and a significant residual stenosis after pre-dilatation are considered as a contraindication to DCB-only strategy[30]. In these cases, the implantation of a DES is considered mandatory. It has been suggested that de novo coronary lesions treated with DCB show persistent anatomical and physiological patency with plaque redistribution and vessel remodelling at invasive follow-up.

Indeed, Poerner et al. conducted an invasive follow up at 6-months after 47 DCB-only fractional flow reserve (FFR)-guided angioplasties using Optical coherence tomography (OCT). They found a trend toward positive vessel remodelling with late lumen enlargement (LLE) in DCB-only PCI, postulating that clinically silent type A and B dissections were mostly healed[38]. These results were corroborated by Ann et al. who performed an invasive follow-up with ultrasound-virtual histology (IVUS-VH) to assess plaque composition. They discovered that after DCB-only PCI, the mean vessel area and lumen area significantly increased after 9 months, while the percent of atheroma volume decreased significantly (although plaque compositions remained unchanged)[39]. Interestingly, a recent study from Yamamoto et al. showed that the presence of medial dissection with an arc > 90° after DCB treatment predicted LLE at follow-up[40].

However, the use of DCB for complex lesions, such as calcified plaque remains a controversial indication. Calcified lesions are known to have higher incidences of restenosis and stent thrombosis than non-calcified lesions following PCI with DES. An autoptic study revealed that inter-strut distance frequently observed in stent struts malapposition or stent underexpansion in heavily calcified plaque leads to a local drug gradient, which is the primary mechanism of DES restenosis[41].

Moreover, PCI using DCB after preparation of calcified with rotational atherectomy in patients with calcified de novo lesions appears to be safe as shown by Rissanen et al. This strategy could offer many advantages over stenting in calcified lesions, such as lower risk of application of an undersized stent[42].

Conversely, as underlined by Nakamura et al.[18], DES are more commonly used including diffuse, calcified lesions, long-balloon-treated and debulking device-used lesions, or preprocedural smaller Minimal Lumen Diameter (MLD). These lesion features result in a lower probability of optimal lesion preparation and a higher risk of dissection and acute recoil after pre-dilatation. Given these considerations, we should move beyond the concept of *'Leave nothing behind'* and adopt a more pragmatic approach (i.e., *'Leave as little as possible behind'* strategy). This approach combines the advantages of using stents in terms of feasibility and safety concerning dissections or calcified lesions, while still allowing long segments of vessels to remain free from a metal cage. Notably, most studies on DCB included a variable proportion of patients treated with the hybrid approach, with some studies reporting rates as high as 70%.

Moreover, it has been proposed that treatment with DCB may preserve endothelial function. The administration of acetylcholine resulted in less pronounced vasoconstriction in peri-treated region in DCB-treated vessels than in DES-treated vessels[43]. Additionally, DCB-treated vessels exhibit a similar vasomotor function compared to normal coronary segments[44].

Limitations

The main limitation of our meta-analysis is that we included non-randomized clinical trials. Therefore, it will be necessary to wait for the evidence from numerous ongoing randomized trials before drawing definitive conclusion on the safety and efficacy of DCB-only angioplasty in large coronary vessel. Moreover, this is a summary and not patient level meta-analysis. Another limitation is the heterogeneity of the composite endpoint definition of TLF. Nevertheless, we decided to also include this outcome in our study, despite its intrinsic methodological limitation. Moreover, even if DCB do not have a "class effect", we have not conducted a specifical sub-analysis according to each device or antiproliferative drug due to the lack of data.

Conclusions

This is the largest comprehensive meta-analysis summarizing currently available data on feasibility, safety, and efficacy of DCB strategy for treating de novo lesions in large coronary vessels. Despite the lack of evidence from large, randomized trials, we can speculate that DCB PCI in large coronary vessels, especially if assisted by a thoughtful use of DES, is safe and effective.

Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions
CG, LB, GT, FC and LM conceptualized the study and provided supervision; FG, EG and AF conducted the search; IM, GP, VV, SE contacted authors for additional information not reported in published articles; FG, EG and AF extracted data and performed the quality assessment appraisal; CG, LB, GT, FC, LM, MR and SC contributed to the interpretation of the results; MR and SC critically revised the text. All authors provided critical feedback on drafts and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Additional information
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