REC Interv Cardiol. 20XX;XX(X):XX-XX
https://doi.org/10.24875/RECICE.M26000612

Editorial

Drug-coated balloons for de novo coronary lesions: are we ready for a leave-nothing-behind strategy?

Balones liberadores de fármaco para lesiones coronarias de novo: ¿estamos preparados para no dejar nada atrás?

Juan F. Iglesias*

Department of Cardiology, Geneva University Hospitals, Geneva, Switzerland

SEE RELATED CONTENT:
https://doi.org/10.24875/RECICE.M26000583

The evolution of percutaneous coronary intervention (PCI) has been driven by sustained efforts to improve long-term clinical outcomes while minimizing device-related complications. Newer-generation drug-eluting stents (DESs) represent the contemporary standard of care across all patient and lesion subsets owing to their excellent performance.[1,2] However, despite major technological advances, the fundamental limitation of DESs remains unchanged: by leaving behind a permanent metallic implant and causing irreversible vessel caging, DESs impair coronary vasomotion and expose patients to device-related adverse events that accrue over time without attenuation.[3,4] As a result, the interventional cardiology community has pursued alternative strategies to preserve local antiproliferative drug delivery while avoiding the consequences of permanent coronary implants.

Drug-coated balloons (DCBs) represent the most mature embodiment of the "leave-nothing-behind" concept. By delivering antiproliferative agents directly to the arterial wall without leaving a metallic footprint, DCB-PCI offers an attractive alternative to DESs, preserving vessel physiology, reducing vascular inflammation, and decreasing metallic burden, which may mitigate stent-related adverse outcomes and simplify dual antiplatelet therapy (DAPT).[5] Despite a compelling biological rationale, accumulating clinical evidence, and growing enthusiasm, the role of DCB-PCI in de novo coronary artery disease (CAD) remains debated. In native small-vessel disease, DCB-PCI may reduce major adverse cardiovascular events (MACE), but not target lesion failure, compared with DESs at 3 years, although these findings derive from a small number of noninferiority randomized controlled trials (RCTs) with modest sample sizes, limited follow-up, surrogate angiographic endpoints, and comparisons with first-generation DESs.[6] In native large-vessel CAD, the role of DCB-PCI has recently come under scrutiny after 2 large-scale RCTs reported conflicting results,[7,8] raising concerns about whether DCB efficacy in de novo CAD differs according to vessel size.[7]

Against this background, in a recent article published in REC: Interventional Cardiology, Rinaldi et al. provide the most comprehensive contemporary comparison of DCB-PCI vs DES-PCI for the treatment of de novo CAD.[9] In this study-level meta-analysis of 13 RCTs including a total of 7776 patients with de novo CAD (mean reference vessel diameter [RVD], 2.95 mm; DCB-PCI, 3896 patients) across a broad spectrum of clinical presentations (~50% with acute coronary syndrome) and lesion subsets, the primary endpoint of target lesion revascularization (TLR) did not differ between DCB-PCI and DES-PCI over a mean follow-up of ~2 years. No significant differences were observed in death, myocardial infarction, target vessel revascularization (TVR), or MACE. These findings were consistent across prespecified subgroup and meta-regression analyses, including analyses according to drug type, clinical presentation, DAPT duration, follow-up duration, and RVD. DCB-PCI was associated with a 35% relative reduction in the risk of major bleeding compared with DES-PCI. Angiographic follow-up at ~8 months reflected the mechanistic differences between the technologies, with DESs achieving a lower percent diameter stenosis, a greater minimum luminal diameter, and superior net luminal gain, whereas DCBs demonstrated lower late lumen loss, without significant differences in binary restenosis.

Although previous meta-analyses have compared DCBs with DESs in de novo CAD,[10-13] this study stands out as the largest to date and the first one to include the most recent large-scale RCTs evaluating DCB-PCI in large-vessel CAD,[7,8] thereby substantially expanding the evidence base in this setting. Nevertheless, the conclusion that DCB-PCI provides comparable long-term ischemic outcomes and a lower risk of major bleeding than contemporary DESs warrants careful interpretation.

Several methodological limitations should be acknowledged. First, the meta-analysis exhibits substantial heterogeneity in the primary endpoint, largely driven by the REC-CAGEFREE I trial,[7] whose failure to demonstrate noninferiority may not be fully explained by trial design alone. The absence of significant differences in TLR may therefore reflect the pooling of trials with heterogeneous designs—including strategy vs device comparisons, noninferiority vs superiority frameworks, and differing primary endpoints and vessel-size definitions—as well as heterogeneous patient populations, lesion subsets, and several DCB platforms. This heterogeneity limits the interpretability of the pooled estimates, and the absence of a statistically significant difference should not be interpreted as evidence of comparable efficacy between DCBs and DESs across all clinical settings. Second, because this was a study-level

* **Corresponding author.**
E-mail address: juanfernando.iglesias@hug.ch (J.F. Iglesias).
𝕏 @JuanFIglesias1
Juan F. Iglesias

Online 12 August 2026.

Please cite this article in press as: Iglesias JF. Drug-coated balloons for de novo coronary lesions: are we ready to leave nothing behind? *REC Interv Cardiol*. 2026. https://doi.org/10.24875/RECICE.M26000612.

meta-analysis, adjustment for confounders and patient-level subgroup analyses was limited, and the subgroup findings should not be overinterpreted. Accordingly, the consistent treatment effect across vessel sizes, based on meta-regression using mean RVD rather than individual patient data, should be interpreted cautiously. The absence of a significant interaction does not exclude a clinically meaningful effect of vessel size, particularly given the trend toward a higher risk of TLR with DCBs in trials enrolling patients with larger vessels. Third, procedural variability across trials introduces additional uncertainty. Lesion preparation varied considerably, with modified balloons used in more than 60% of cases in some studies, potentially attenuating between-group differences. Bailout stenting (BOS) was required in up to 20% of patients in selected trials, which may have biased the results toward apparent equivalence. This is relevant because BOS is protocol-defined in strategy trials but reflects procedural failure in device-comparison studies. Fourth, all included RCTs enrolled patients in whom both treatment strategies were considered technically feasible and clinically appropriate, limiting extrapolation to unselected all-comer populations. Finally, whether clinically meaningful differences exist between paclitaxel- and sirolimus-coated balloons remains uncertain despite the absence of a significant interaction according to drug type, because the available evidence is largely dominated by paclitaxel devices and head-to-head outcome RCTs are lacking.

A novel technology merits consideration as an alternative to the established standard of care only if it demonstrates a comparable safety and efficacy profile while ideally offering additional benefits. In this regard, this meta-analysis raises several unresolved questions. First, although no statistically significant differences were detected in overall ischemic outcomes, the point estimates for both TLR and TVR were numerically higher after DCB-PCI, by 24% and 39%, respectively, and the confidence intervals remained compatible with a clinically meaningful increase in repeat revascularization. Thus, the statistically neutral findings should not be interpreted as evidence of clinical equivalence. Two additional analyses corroborated this concern. In a sensitivity analysis excluding the study in which a substantial proportion of control patients received paclitaxel-eluting stents, potentially inflating DCB performance, DCBs were associated with a significantly higher risk of TVR than DESs. A meta-regression further demonstrated a progressive increase in the risk of TLR with DCBs in more recent trials, possibly reflecting the inclusion of broader patient populations, larger vessels, and more complex lesions. Notably, the open-label design of all included trials may have introduced surveillance bias and lowered the threshold for repeat revascularization in the DCBs arm, thus limiting the interpretation of these findings. Follow-up was relatively short, whereas potential benefits of DCBs in reducing DES-related adverse events may emerge only during longer-term follow-up. Finally, despite the large sample size, the analysis was likely underpowered to detect modest but clinically meaningful differences in hard endpoints such as cardiac death and vessel thrombosis.

Second, the reduction in major bleeding is biologically plausible and consistent with the potential of DCBs to enable shorter DAPT than DESs. However, this finding should be considered hypothesis-generating because no significant treatment interaction according to DAPT duration was observed. The reduction in bleeding appears to have been influenced by trials in which patients treated with DCBs received a shorter DAPT regimen than those treated with DES. Consequently, the apparent bleeding benefit may reflect differences in trial design and antiplatelet protocols, particularly in studies with greater between-group differences in DAPT duration. Ongoing RCTs—DEBATE (NCT04814212), DCB-HBR (NCT05221931), and PICCOLETTO IV-EPIC 38 (NCT06535568)—will determine whether less intensive antiplatelet strategies after DCB-PCI translate into a net clinical benefit by reducing bleeding without compromising ischemic protection.

Where, then, does DCB-PCI fit into the contemporary treatment of de novo CAD? This meta-analysis suggests that DCBs should be considered a treatment option for selected patients and lesions rather than providing definitive evidence supporting their routine use as an alternative to DESs in de novo CAD. Further RCTs, particularly in large-vessel de novo CAD, are needed to better define which patients and lesion subsets derive the greatest benefit from DCB-PCI. Longer-term follow-up of DCB-PCI trials is warranted to determine whether the observed signal for repeat revascularization attenuates over time or differs according to patient and lesion characteristics. In contrast to DES implantation, successful DCB-PCI is highly dependent on meticulous lesion preparation and procedural technique. Whether similar outcomes are reproducible in routine clinical practice beyond experienced centres remains uncertain. Therefore, broader adoption of DCB-PCI for de novo CAD will require addressing several key challenges, including refinement of patient and lesion selection, standardization of lesion preparation, implementation of a structured procedural workflow incorporating intravascular imaging and coronary physiology, and optimization of coronary dissection management to minimize BOS while preserving a "leave-nothing-behind" strategy.

In conclusion, the meta-analysis by Rinaldi et al.[9] provides valuable insights into the contemporary role of DCBs in de novo CAD while raising unanswered questions regarding patient and lesion selection, optimal antiplatelet strategies, and the long-term efficacy profile of DCBs. Until further randomized evidence becomes available, coronary revascularization in de novo CAD should rely on the complementary use of DES, DCB, and bioresorbable scaffolds, alone or in hybrid combinations, according to individual patient and lesion characteristics and the clinical context in which each strategy has been validated. Within the conceptual framework of reducing overall stent burden, lesion preparation should remain a fundamental prerequisite for all PCI strategies, with device selection viewed as a downstream decision rather than as a competing upfront paradigm. The journey toward implementing a default metal-free PCI strategy for de novo CAD is far from complete. The ambition should not simply be to leave nothing behind, but to leave no unanswered questions behind.

FUNDING

None declared.

CONFLICTS OF INTEREST

J.F. Iglesias reports unrestricted research grants paid to the institution by Biotronik, Concept Medical, Terumo Corp., and the De Reuter Foundation, outside the submitted work; consulting fees from Cordis, outside the submitted work; speaker fees from Cordis, Concept Medical, Penumbra Inc., and Teleflex, outside the submitted work; support for attending meetings and/or travel from Biotronik, Cordis, and Medtronic, outside the submitted work; and participation on the data safety monitoring boards of the Co-STAR (NCT04870424) and REGENERATE-COBRA (NCT05711849) trials.

REFERENCES

1. Byrne RA, Rossello X, Coughlan JJ, et al.; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720-3826.
2. Vrints C, Andreotti F, Koskinas KC, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45:3415-3537.

Please cite this article in press as: Iglesias JF. Drug-coated balloons for de novo coronary lesions: are we ready to leave nothing behind? *REC Interv Cardiol*. 2026. https://doi.org/10.24875/RECICE.M26000612.

3. Madhavan MV, Kirtane AJ, Redfors B, et al. Stent-Related Adverse Events >1 Year After Percutaneous Coronary Intervention. *J Am Coll Cardiol*. 2020;75:590-604.
4. Kufner S, Ernst M, Cassese S, et al.; ISAR-TEST-5 Investigators. 10-Year Outcomes From a Randomized Trial of Polymer-Free Versus Durable Polymer Drug-Eluting Coronary Stents. *J Am Coll Cardiol*. 2020;76:146-158.
5. Fezzi S, Serruys PW, Cortese B, et al. Indications for Use of Drug-Coated Balloons in Coronary Intervention: Academic Research Consortium Position Statement. *J Am Coll Cardiol*. 2025;86:1170-1202.
6. 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.
7. Gao C, He X, Ouyang F, et al.; REC-CAGEFREE I Investigators. 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.
8. Spaulding C, Krackhardt F, Bogaerts K, et al.; SELUTION DeNovo Investigators. 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.
9. Rinaldi R, Bujak K, Occhipinti G, et al. Drug-coated balloons versus drug-eluting stents for de novo coronary lesions: a systematic review and meta-analysis. *REC Interv Cardiol*. 2026. https://doi.org/10.24875/RECICE.M26000583.
10. Niu J, Wang K, Wang W, et al. Drug-Coated Balloons versus Drug-Eluting Stents for the Treatment of De Novo Coronary Artery Disease: A Meta-Analysis of Randomized Controlled Trials. *Rev Cardiovasc Med*. 2024;25:446.
11. O'Callaghan D, Rai H, Giacoppo D, et al. Drug Coated Balloons Versus Drug-Eluting Stents in Patients With De Novo Coronary Artery Disease. *Catheter Cardiovasc Interv*. 2025;106:1843-1853.
12. Wańha W, Ullah I, Gurgoglione FL, et al. Comparison of Percutaneous Intervention With Drug Coated Balloons and Drug Eluting Stents for De Novo Coronary Artery Disease: CIRCE, a Systematic Review and Meta-Analysis. *Am J Cardiol*. 2026;271:98-105.
13. Yu Y, Jiao YM, Li Y, Zhang M, Song GY, Yin CQ. Drug-Coated Balloons Versus Other Percutaneous Coronary Intervention Strategies in De Novo Coronary Artery Disease: A Systematic Review, Meta-Analysis With Trial Sequential Analysis. *Cardiovasc Ther*. 2026;2026:5568664.

Please cite this article in press as: Iglesias JF. Drug-coated balloons for de novo coronary lesions: are we ready to leave nothing behind? *REC Interv Cardiol*. 2026. https://doi.org/10.24875/RECICE.M26000612.