

Drug-Coated Balloons in Contemporary Coronary Interventions: A Systematic Review of Current Evidence

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Abstract

Drug-coated balloons (DCBs) are a percutaneous coronary intervention technology that enables rapid and homogeneous delivery of antiproliferative agents to the vessel wall without leaving a permanent metallic scaffold. With the accumulation of clinical evidence and the development of new-generation devices, the use of DCBs has expanded beyond the treatment of in-stent restenosis (ISR) to include a wide range of clinical settings such as small vessel disease, bifurcation lesions, acute coronary syndromes (ACS), and chronic total occlusions (CTO). Contemporary DCB platforms are primarily based on paclitaxel- or sirolimus-coated technologies, while advances in carrier systems and coating techniques have improved drug transfer efficiency, safety, and long-term outcomes. Appropriate lesion preparation, optimal device selection, and the integration of intravascular imaging techniques remain essential determinants of procedural success. Randomized trials support DCB use in ISR and in small-vessel coronary disease, although current European guidelines favor repeat drug-eluting stent (DES) implantation over DCB for restenosis of DES. Evidence in bifurcation lesions, ACS, and CTO is more limited and derives largely from trials powered for angiographic rather than clinical endpoints; in unrestricted de novo lesions, a DCB-based strategy did not meet non-inferiority against DES in the REC-CAGEFREE I trial. This review summarizes the fundamental principles of DCB technology, contemporary device characteristics, technical considerations, major clinical indications, and the most relevant evidence from current literature. DCB technology is an established component of the "leave nothing behind" strategy in selected indications, whereas its role in several de novo settings remains to be defined by adequately powered randomized trials with long-term clinical endpoints.

Keywords: Angioplasty-balloon-coronary; coronary artery disease; coronary restenosis; percutaneous coronary intervention.

Güncel Koroner Girişimlerde İlaç Kaplı Balonlar: Güncel Kanıtların Sistematiik Derlemesi

Özet

İlaç kaplı balonlar (İKB), antiproliferatif ajanın damar duvarına hızlı ve homojen biçimde aktarılmasını sağlayan ve geride kalıcı metalik iskele bırakmayan bir perkütan koroner girişim teknolojisidir. Klinik kanıtların birikmesi ve yeni kuşak cihazların geliştirilmesiyle birlikte İKB kullanımı, stent içi restenoz (SİR) tedavisinin ötesine geçerek küçük damar hastalığı, bifurkasyon lezyonları, akut koroner sendromlar ve kronik total oklüzyonlar gibi geniş bir klinik yelpazeye yayılmıştır. Güncel İKB platformları esas olarak paklitaksel veya sirolimus kaplı teknolojilere dayanmakta; taşıyıcı sistemler ve kaplama tekniklerindeki gelişmeler, ilaç transfer verimliliğini, güvenilirliği ve uzun dönem sonuçları iyileştirmektedir. Uygun lezyon hazırlığı, doğru cihaz seçimi ve intravasküler görüntüleme yöntemlerinin kullanımı, işlem başarısının temel belirleyicileri olmayı sürdürmektedir. Randomize çalışmalar, İKB'nin SİR ve küçük damar hastalığındaki kullanımını desteklemektedir; bununla birlikte güncel Avrupa kılavuzları, ilaç salımlı stent restenozunda İKB yerine yeniden ilaç salımlı stent implantasyonunu önermektedir. Bifurkasyon lezyonları, akut koroner sendromlar ve kronik total oklüzyonlara ilişkin kanıtlar daha sınırlıdır ve büyük ölçüde klinik sonuçları yerine anjiyografik sonuçları açısından güçlendirilmiş çalışmalardan elde edilmiştir. Damar çapı kısıtlaması bulunmayan de novo lezyonlarda ise İKB temelli strateji, REC-CAGEFREE I çalışmasında ilaç salımlı stente karşı non-inferiorite kriterini karşılayamamıştır. Bu derleme, İKB teknolojinin temel ilkelerini, güncel cihaz özelliklerini, teknik hususları, başlıca klinik endikasyonları ve mevcut literatürdeki en ilgili kanıtları özetlemektedir. İKB teknolojisi, seçilmiş endikasyonlarda "geride hiçbir şey bırakmama" stratejisinin yerleşmiş bir bileşenidir; buna karşılık çeşitli de novo durumlardaki rolünün, uzun dönem klinik sonuçlarını değerlendirmek için yeterli güce sahip randomize çalışmalarla tanımlanması gerekmektedir.

Anahtar sözcükler: Koroner balon anjiyoplasti; koroner arter hastalığı; koroner restenoz; perkütan koroner girişim.

Cite This Article: Gülyiğit H, Koca Ç, Gürsoy MO. Drug-coated Balloons in Contemporary Coronary Interventions: A Systematic Review of Current Evidence. Koşuyolu Heart J 2026;29(3):219–227.

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Submitted: July 01, 2026

Revised: August 12, 2026

Accepted: August 22, 2026

Available Online: October 21, 2026



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Introduction

Drug-coated balloons (DCBs) have become increasingly common devices in the invasive treatment of obstructive coronary artery disease. They eliminate the need to leave a permanent metallic scaffold in the vessel by ensuring rapid and homogeneous delivery of the antiproliferative drug into the vessel wall during balloon inflation.^[1]

Inadequate sample sizes in existing clinical trials and inconsistencies in endpoint definitions have delayed the inclusion of this technology in guidelines. Various consortia have been established to ensure standardization in clinical research, clarify study designs, and harmonize endpoints under a common terminology.^[2] However, the fact that meta-analyses and comprehensive studies on this subject remain limited increases the need for guiding documents for interventional cardiologists regarding DCB use. This review aims to address the uncertainties surrounding DCBs, synthesize contemporary evidence, and provide a concise summary of the current literature to contribute meaningfully to the field.

Design and Technological Features of DCBs

At present, the primary molecules loaded onto the balloon surface are Paclitaxel and Sirolimus. On balloon inflation, the active drug is transferred to the vascular surface and penetrates the vessel wall. Here, it inhibits the migration of smooth muscle cells and fibroblasts from the media to the intima, as well as their proliferation and extracellular matrix synthesis.^[3] Local drug delivery has been used for approximately three decades. Early laboratory and animal models demonstrated that Paclitaxel, an agent used in oncological treatments, successfully suppressed neointimal proliferation.^[4] The homogeneity and efficiency of the antiproliferative drug transfer to the target tissue play a critical role in the efficacy of DCBs. The most important technological components governing this transfer are hydrophilic carrier systems (excipients/matrix structures).^[5] In the earliest successful examples, iopromide, an X-ray contrast agent, was used as a carrier matrix to facilitate the transition of paclitaxel into the tissue. Today, the most frequently preferred hydrophilic carrier agents are urea, polyethylene glycol, polyvinylpyrrolidone, and hyaluronic acid.^[6] Another core component of DCBs is the adhesive, biocompatible, and bioresorbable coating polymers that retain the drug on the surface and control its release. Due to its established safety profile in Drug-eluting stent (DES) technology, Sirolimus (mTOR inhibitors) has also found widespread application in this field.^[7]

Paclitaxel-Coated Balloon Systems

Paclitaxel is derived from the bark of the Pacific yew tree (*Taxus brevifolia*). The safety of this cytotoxic agent in coronary applications has been demonstrated by its use at levels well below systemic toxic doses (one coronary balloon contains approximately 0.4 mg of the drug).^[8] The prominent features of paclitaxel-coated DCBs are detailed below:

- Paccocath and SeQuent please: Historically the first technology developed, Paccocath integrated paclitaxel into a

matrix containing iopromide spacers. SeQuent Please, an advanced version of this structure, rapidly transfers approximately 80% of the drug to the vessel wall during inflation.^[9,10]

- Agent: It is the first and only DCB system to recently receive FDA approval for the treatment of in-stent restenosis (ISR) in the United States. Despite containing a lower dose compared to competitor platforms, its specialized crystallization technology called TransPax (acetyl tributyl citrate - excipient) enables it to achieve vascular tissue levels comparable to higher-dose balloons.^[11]
- Dior II: Manufactured with the addition of Shellac, a natural resin, in its second generation. The hydrophilic shellac structure swells upon contact with body fluids, increasing drug transfer to the tissue by 2–20 times, even with short inflation times of 30–45 s.^[12]
- Other systems: While IN.PACT Falcon utilizes a urea-based hydrophilic matrix, Pantera Lux provides effective protection in small vessels with the help of a biocompatible BTHC excipient. On the other hand, RESTORE features a unique SAFEPAX shellac-ammonium salt formulation that minimizes the risk of drug loss.^[13–15]

Sirolimus-Coated Balloon (SCBs) Systems

Sirolimus (rapamycin) is a cytostatic agent that blocks the proliferation of smooth muscle cells at the G1/S phase transition by inhibiting the activation of mTOR, a specific kinase regulating the cell cycle, via the FKBP12 protein. Its lower tissue penetration capability compared to paclitaxel and the reversible character of its cellular binding have driven manufacturers to develop specialized carrier formulations.^[16]

- MagicTouch: Encapsulates sirolimus molecules within nanoparticles composed of phospholipid layers. This technology maximizes tissue bioavailability by reducing drug loss during delivery.^[17]
- Selution: The system relies on poly(lactic-co-glycolic acid) micro-reservoirs that undergo biodegradable matrix breakdown to elute sirolimus, thereby replicating the pharmacological release profile of state-of-the-art Limus-based DES.^[18]
- SeQuent Please SCB: Contains crystalline sirolimus at a high dosage with a BHT additive. Literature demonstrates that nearly half of the transferred drug payload remains detectable within the arterial wall a month after the initial intervention.^[19]
- Mozec Sirolimus-Eluting Balloon and Biolimus A9: The Mozec SEB provides 1-month tissue protection through solid lipid nanospheres smaller than 500 nm. The DCB platform carrying Biolimus A9, a derivative 10 times more lipophilic than sirolimus, utilizes a polyethylene oxide matrix and has demonstrated head-to-head angiographic success with paclitaxel-based DCBs in cases of in-DES restenosis.^[20,21]

The choice of DCB in interventional vascular treatments should be optimized according to the anatomical features of the target lesion and the desired cellular response. In this context, due to its highly lipophilic nature, strong tissue pen-

Table 1. Potential advantages of DCB over DES and their principal counterpoint^[24]

Evaluation parameter	Potential advantages of DCB technology	Caveat/Counterpoint
Vascular Physiology	Preserves the physiological vasoreactive compliance and natural motion of epicardial coronary arteries.	Offset by the absence of acute lumen gain; elastic recoil after predilatation may mandate bail-out stenting.
Future Revascularization	Maintains full anatomical eligibility for subsequent CABG by leaving the native vessel un-stented.	Anatomically plausible, but no randomized trial has assessed subsequent CABG feasibility or outcome as an endpoint.
Endothelialization and DAPT	Accelerates arterial wall endothelial coverage, facilitating a substantially abbreviated course of DAPT.	Abbreviated DAPT after DCB-only PCI rests on consensus opinion, registry data, and pathophysiological reasoning, not on dedicated randomized trials of DAPT duration.
Complex Subgroups	Provides optimized outcomes in DES-suboptimal cohorts, including small-vessel coronary disease, diffuse lesions, diabetic individuals, and patients with HBR.	Demonstrated principally in small-vessel disease; in de novo lesions without diameter restriction, REC-CAGEFREE I did not meet non-inferiority against DES at 24 months.
Biocompatibility	Eliminate the risk of chronic polymer-induced hypersensitivity reactions and late-term stent thrombosis by avoiding permanent metallic scaffolding.	Applies only to the DCB-treated segment; bail-out stenting, required in a minority of procedures, reintroduces these risks.

CABG: Surgical bypass grafting; DAPT: Dual antiplatelet treatment; DCB: Drug-coated balloon; DES: Drug-eluting stent; HBR: High bleeding risk.

etration, and cytotoxic mechanism of action, paclitaxel has generally been preferred in lower extremity peripheral arterial interventions, in heavily calcified or fibrotic lesions, and in recurrent coronary ISR with aggressive neointimal hyperplasia.^[3,22,23] Conversely, its broader therapeutic index and cytostatic mechanism have led to sirolimus being proposed for small-vessel lesions, including those in diabetic patients.^[3,22,23] It must be emphasized, however, that these preferences rest largely on mechanistic reasoning rather than on comparative outcome data. Direct head-to-head randomized comparisons remain few, are predominantly powered for angiographic rather than clinical endpoints, and have not established the superiority of either platform: SIBLINT-ISR demonstrated non-inferiority of a crystalline SCB to a paclitaxel-coated balloon in DES-ISR, whereas TRANSFORM I – a mechanistic study of limited size – showed marginally lower late lumen loss with paclitaxel. Device selection therefore remains largely empirical.

Technical Considerations in the Use of DCBs

The potential advantages of DCBs over DES strategies, together with their principal caveats, are summarized in Table 1.^[24] Achieving procedural success with DCBs is heavily contingent upon meticulous and strategic lesion preparation. Predilatation should be performed using semi-compliant or non-compliant (NC) balloons at a 1:1 ratio with the reference vessel diameter (RVD). In this manner, microscopic disruptions created in the intima facilitate the diffusion of the drug into the tissue. If standard balloons remain insufficient in severely calcified lesions, advanced modification methods such as high-pressure NC balloons, cutting balloons, atherectomy devices (rotational/orbital/laser), or intravascular lithotripsy should be utilized.^[25,26] The criteria for successful lesion preparation are as follows:^[2]

- A residual stenosis of less than 30% post-procedure
- A balloon-to- RVD ratio of 1:1
- Achievement of TIMI-3 flow grade
- Absence of flow-limiting dissections (Type A and B dissections are acceptable).

Meticulous predilatation performed under the guidance of intravascular imaging modalities such as intravascular ultrasound or optical coherence tomography has been shown to provide a larger lumen area and improve long-term clinical success compared to angiographic guidance alone.^[27,28] Technically, due to their structural profiles, DCBs may exhibit reduced deliverability compared to standard balloons; this can lead to crossability failure in extremely tortuous, calcified, or distal lesions. Once removed from its packaging, the balloon must not be touched directly and should be delivered to the lesion site and inflated within the maximum transit time specified by the manufacturer to prevent drug loss from the surface. The minimum inflation time varies between 30 and 120 s depending on the device type. An adequate longitudinal safety margin is vital; hence, the DCB should overlap the lesion boundaries by a minimum of 2 mm on each side (totaling 4 mm) to mitigate geographic miss.^[25]

Clinical Indications and Clinical Trial Data

Although the therapeutic efficacy of coronary DCB applications remains most deeply anchored in the management of ISR due to a wealth of historical clinical trials, contemporary interventional cardiology is witnessing an accelerated diversification of their use. Its use has since been investigated in de novo small-vessel lesions, bifurcation lesions, chronic total occlusions (CTO), acute coronary syndromes (ACS), and in patients with diabetes mellitus or at high bleeding risk (HBR). The strength of the supporting evidence differs substantially across these settings, and the following sections are therefore organized accordingly: Section 4.1 addresses indications supported by consistent randomized data and explicit guideline recommendations, whereas Section 4.2 addresses emerging indications for which the evidence base remains preliminary. It should be noted at the outset that no class of recommendation has been assigned to DCB use in bifurcation lesions, ACS, or CTO; for these indications, the available guidance derives from expert consensus documents rather than from guideline recommendation tables.

Table 2. Clinical efficacy and outcomes of drug-coated balloons for in-stent restenosis: A review of key evidence

Study name/ Year	Study objective	Number of patients	Drug-coated balloon brand	Drug name	Study results	Study limitations	Study summary conclusion	Primary endpoint	Follow-up
PACCOCATH ISR I and II / 2006 (ISR I) - 2008 (ISR II)	To evaluate the angiographic and clinical efficacy of paclitaxel-coated balloons versus conventional balloon angioplasty (POBA) in patients with bare-metal stent restenosis (BMS-ISR).	108 patients	Paccocath (Prototype)	Paclitaxel	Late lumen loss at 6 months was significantly lower in the DCB group. TLR at 12 months was 4% versus 43% with POBA.	Relatively small sample size; limited patient population; no direct comparison with newer DES generations.	Paclitaxel-coated balloons markedly reduced restenosis and repeat revascularization versus POBA in BMS-ISR.	In-segment late lumen loss at 6 months	Angiographic 6 months; clinical 12 months (extended follow-up to 5 years)
PEPCAD II / 2009	Comparison of paclitaxel-coated balloon therapy with first-generation paclitaxel-eluting stent implantation in BMS-ISR.	131 patients	SeQuent Please	Paclitaxel	Lower late lumen loss and lower MACE rates with DCB than PES at 12 months.	Used first-generation PES and does not reflect performance of contemporary DES.	Paclitaxel-coated balloon showed superior angiographic and clinical outcomes versus first-generation PES.	In-segment late lumen loss at 6 months	Angiographic 6 months; clinical 12 months
ISAR-DESIRE 3 / 2012	Three-arm comparison of DCB, PES and POBA in patients with DES-ISR.	402 patients	SeQuent Please	Paclitaxel	DCB and PES were superior to POBA; DCB was non-inferior to PES.	Compared against first-generation PES; lesion subgroups not fully homogeneous.	DCB provides efficacy comparable to DES and superior to POBA without adding another stent layer.	Percent diameter stenosis at 6–8 months	Angiographic 6–8 months; clinical 12 months (3-year data reported)
RIBS V / 2014	Direct comparison of DCB and everolimus-eluting stents (EES) in BMS-ISR.	189 patients	SeQuent Please	Paclitaxel	EES achieved larger lumen diameter, but clinical outcomes were similar.	Mandatory angiographic follow-up may have influenced interventions; only 1-year follow-up.	Both DCB and EES were highly effective; EES provided greater acute lumen gain.	Minimal lumen diameter at 9 months	Angiographic 9 months; clinical 12 months
RIBS IV / 2015	Randomized comparison of DCB versus EES in DES-ISR.	309 patients	SeQuent Please	Paclitaxel	EES showed better angiographic outcomes and lower TLR at 1 year.	Diffuse multilayer stent lesions affected follow-up desirable.	EES outperformed paclitaxel-coated balloons in challenging DES-ISR cases.	Minimal lumen diameter at 6–9 months	Angiographic 6–9 months; clinical 12 months (3-year data reported)
AGENT ISR / 2024	To validate safety and efficacy of the Agent paclitaxel-coated balloon versus POBA in DES-ISR.	487 patients	Agent DCB	Paclitaxel	Target lesion failure was significantly lower with Agent DCB than POBA.	Open-label design; lesion preparation techniques were not fully standardized.	Agent DCB significantly reduced target lesion failure and repeat revascularization.	Target lesion failure at 12 months	Clinical 12 months (24-month data reported)
SIBLINT-ISR / 2024–2025	Direct comparison of a new crystalline sirolimus-coated balloon versus conventional paclitaxel-coated balloon in DES-ISR.	258 patients	SeQuent SCB	Sirolimus	Sirolimus-coated balloon was non-inferior to paclitaxel-coated balloon.	Moderate sample size and limited long-term outcome maturity.	New-generation sirolimus-coated balloons were a successful alternative to paclitaxel-coated balloons.	In-segment late lumen loss (non-inferiority design)	Angiographic follow-up; long-term clinical data immature

Table 2. Clinical efficacy and outcomes of drug-coated balloons for in-stent restenosis: A review of key evidence

Study name/ Year	Study objective	Number of patients	Drug- coated bal- loon brand	Drug name	Study results	Study limitations	Study summary conclusion	Primary endpoint	Follow-up
TRANSFORM I / 2024	Head-to-head comparison of two modern DCBs (sirolimus vs. paclitaxel) in restenosis and small-vessel disease.	114 patients	MagicTouch versus Se- quent Please NEO	Sirolimus (phos- pholipid nanocarri- er) versus Paclitaxel	Paclitaxel showed slightly less lumen loss, but both met safety and efficacy goals.	Mechanistic study with limited sample size for hard clinical endpoints.	Outcome depends on both drug type and car- rier/matrix technology.	Imaging-de- rived measure of neointimal response (mechanistic design)	6 months
EASTBOURNE Registry (ISR Sub-analysis) / 2024–2025	Real-world multicenter evaluation of long-term safety and efficacy of sirolimus-coated balloons, especially in ISR.	2123 patients (entire cohort)	MagicTouch	Sirolimus	Low TLR and stent thrombosis rates with favorable safety profile.	Registry study without a direct DES or PCB control group.	Real-world data support good safety and low failure rates in complex ISR.	Target lesion re- vascularization	12 months (reg- istry; longer-term follow-up reported)

BMS: Bare-metal stent; DCB: Drug-coated balloon; DES: Drug-eluting stent; EES: Everolimus-eluting stent; ISR: In-stent restenosis; MACE: Major adverse cardiac events; PCB: Paclitaxel-coated balloon; PES: Paclitaxel-eluting stent; POBA: Plain old balloon angioplasty; SCB: Sirolimus-coated balloon; TLR: Target lesion revascularization.

Established Indications: Consistent Randomized Evidence

Treatment of ISR

The definition of ISR encompasses a minimum 50% luminal narrowing located inside the stented zone or within the adjacent 5 mm proximal or distal edges following successful PCI, an adverse event observed in roughly 5–10% of the overall interventional patient volume.^[29] While the bare-metal stent (BMS)-ISR phenotype is typically characterized by diffuse neointimal hyperplasia, the DES-ISR phenotype stems from a local insufficiency of antiproliferative drugs or late-stage focal neoatherosclerosis, making its treatment more complex. In clinical trials, DCB therapy has consistently outperformed plain old balloon angioplasty (POBA) and BMS. Against second-generation DES, however, results diverge by ISR subtype: outcomes are broadly comparable in BMS-ISR, whereas in DES-ISR repeat DES implantation has proved more effective at preventing target lesion revascularization (TLR).

Table 2 below summarizes the landmark randomized controlled trials comparing the clinical efficacy of DCBs in ISR against POBA and different generations of stents (BMS/DES). In addition, trials comparing sirolimus- and paclitaxel-eluting DCBs in ISR have been included in Table 2.

Current guidelines do not treat the two strategies as equivalent across all ISR subtypes. The 2024 ESC Guidelines for the management of chronic coronary syndromes recommend implantation of a DES in preference to a DCB for the treatment of in-DES restenosis (Class I, Level of Evidence A). This recommendation was informed principally by the DAEDALUS pooled analysis, in which repeat DES implantation reduced TLR at 3 years more effectively than paclitaxel-coated balloons in DES-ISR, while all-cause death and myocardial infarction did not differ between arms. In BMS-ISR, by contrast, the two strategies remain broadly equivalent.^[8,22,30] In BMS-ISR, DCB therapy is frequently preferred because it achieves comparable angiographic and clinical results without imposing an additional metal layer on the vessel. However, in more aggressively progressing DES-ISR, a distinct balance exists between the two methods. Although the implantation of a new-generation DES provides a larger acute lumen gain through mechanical scaffolding, thereby reducing the need for TLR in the early phase (the 1st year) to a greater extent than DCB, it creates a “sandwich effect” (dual-layer metal) in that region over the long term, which increases chronic inflammation, neoatherosclerosis, and the risk of late stent thrombosis. Because a DCB leaves no additional permanent metallic layer, it avoids these theoretical long-term mechanical and thrombotic concerns. On the strength of this rationale – rather than of demonstrated superiority in randomized comparisons – a DCB-based strategy may remain a reasonable option in selected DES-ISR presentations, particularly focal (short) restenosis and vessels already carrying multiple stent layers, in which the addition of further metal is undesirable. This position is not at present reflected in a guideline recommendation and should be regarded as individualized clinical judgment.^[2,22]

Small Vessel Disease (SVD)

Approximately one-third of all percutaneous interventions are executed in narrow coronary segments where the RVD is below 2.75 mm. In these delicate structures, DES deployment introduces a heightened propensity for late-term stent thrombosis and recurrent ISR; this is primarily driven by an exaggerated foreign body response, excessive metal-to-vessel ratio, and an already compromised anatomical caliber. DCB therapy addresses these limitations by delivering an antirestenotic agent without leaving a permanent implant, and therefore represents a therapeutic alternative to conventional DES in SVD.

The most important clinical evidence in this field is the BASKET-SMALL 2 trial. Among the 758 randomized patients, 155 (20%) presented with HBR. These HBR patients exhibited significantly higher mortality at 3 years (hazard ratio [HR], 3.09; 95% confidence interval [CI], 1.78–5.36; $p < 0.001$). Overall, major bleeding event rates were low but tended to be lower in the DCB group compared to the DES group (1.6% vs. 3.7%; $p = 0.064$). While major bleeding rates were comparable between DCB and DES in HBR patients (4.5% vs. 3.4%), they were less frequent with DCB than with DES in non-HBR patients (0.9% vs. 3.8%). Regarding efficacy, no significant differences in major adverse cardiac events (MACE) were observed between DCB and DES, regardless of baseline bleeding risk (HBR: HR, 1.16; 95% CI, 0.51–2.62; $p = 0.719$ vs. non-HBR: HR, 0.96; 95% CI, 0.62–1.49; $p = 0.863$).^[31]

The RESTORE SVD Trial is a multicenter, randomized study that compared head-to-head the efficacy of a new-generation paclitaxel DCB against a second-generation everolimus-eluting stent (EES), which is considered the gold standard, in small coronary vessel lesions (RVD < 2.75 mm). Evaluating the primary endpoint of the study, the in-segment late lumen loss at 9 months, clearly confirmed the non-inferiority of DCB compared to stent therapy (non-inferiority $p < 0.001$), but did not show a statistically significant difference between the two strategies in terms of angiographic superiority (superiority $p = 0.72$). According to the 2-year clinical surveillance data demonstrating the long-term safety profile of the study, MACE rates (6.3% vs. 5.3%, $p = 0.75$) and the need for TLR (3.6% vs. 2.6%, $p = 0.65$) were found to be statistically completely equivalent. Taken together, these p-values demonstrate that DCB is an effective alternative for the treatment of SVD, providing similar angiographic and clinical success to a new-generation DES.^[32]

The PICCOLETO II Randomized Clinical Trial is a multicenter, randomized trial comparing the clinical and angiographic performance of a new-generation paclitaxel-coated balloon (Elutax SV) versus a second-generation Xience EES in small coronary vessel lesions (RVD < 2.75 mm). When the primary endpoint of the study, the in-segment late lumen loss at 6 months, was analyzed, a remarkably low loss was observed in the Elutax SV DCB group, whereas this value was higher in the Xience EES group. This clearly demonstrated that the DCB was angiographically superior to the stent in preserving the lesion area (superiority $p = 0.03$). In parallel, the minimum lumen diameter at 6 months was significantly wider in the DCB arm ($p = 0.011$). When the MACE rates at the end of the 12-month clinical follow-up were

analyzed, reasonable rates of 5.6% in the DCB group and 7.5% in the EES group were obtained, and no statistically significant difference was observed between the two treatment strategies regarding clinical safety ($p = 0.55$). In summary, these p-values reveal that the new-generation Elutax SV DCB is not only a safe alternative in the treatment of SVD but also provides superior angiographic outcomes (less late lumen loss) compared to a gold-standard DES without leaving a permanent metallic scaffold in the vascular structure.^[33]

Taken together, these three randomized trials indicate that new-generation DCBs in SVD achieve results non-inferior to – and, for individual platforms, angiographically better than – contemporary DES in terms of late lumen loss, without leaving a permanent metallic scaffold. All three, however, were powered for angiographic surrogate endpoints rather than for hard clinical outcomes. Consensus documents, including the report of the International DCB Consensus Group, accordingly regard DCBs as a reasonable “stent-free” alternative for de novo small-vessel lesions in which adequate lesion preparation has been achieved.^[22,30]

These favorable results should not, however, be extrapolated to de novo lesions in general. REC-CAGEFREE I, the largest randomized trial in this field to date, enrolled 2,272 patients with de novo, non-complex lesions without any restriction on vessel diameter and compared paclitaxel-coated balloon angioplasty with rescue stenting against intended second-generation DES implantation. Rescue stenting was required in 9.4% of the DCB arm, and at 24 months the device-oriented composite endpoint occurred in 6.4% of the DCB group versus 3.4% of the DES group; the pre-specified non-inferiority criterion was not met. A significant interaction with RVD was observed, supporting the view that the benefit of a DCB-only strategy is confined to smaller vessels rather than being generalizable across de novo lesions.^[34]

Emerging Indications: Limited or Preliminary Evidence

Bifurcation Lesions

PCI for coronary bifurcation lesions represents one of the most complex areas of interventional cardiology due to the technical necessity of preserving both the main branch (MB) and the side branch (SB). Traditional two-stent strategies (provisional, Culotte, DK-Crush, etc.) carry a high risk of ISR and malapposition (incomplete apposition of the stent against the vessel wall), particularly at the side-branch ostium. In these anatomically challenging regions, DCBs stand out as a rational treatment option to reduce the permanent metallic scaffold burden.

The PEPCAD-BIF Trial is a randomized study comparing the application of a paclitaxel-coated balloon (DCB) to the side-branch ostium versus conventional POBA after stenting the MB in coronary bifurcation lesions. The in-segment late lumen loss at 9 months was significantly lower in the DCB group at 0.13 mm compared to 0.51 mm in the plain balloon group, proving a clear superiority of the DCB in side-branch angiographic success ($p = 0.013$).^[35]

BIOLUX-I assessed the feasibility of a hybrid strategy combining an EES in the MB with a paclitaxel-coated balloon at the side-branch ostium. It was a prospective, single-arm, multicenter study that enrolled 35 patients at five Australian sites, with angiographic and intravascular ultrasound assessment at 9 months and clinical follow-up to 12 months. The primary endpoint, side-branch late lumen loss, was 0.10 ± 0.43 mm, and no binary restenosis was observed.^[36] Because the study had no control arm, it establishes feasibility and short-term safety only and permits no comparison with conventional kissing-balloon or plain-balloon treatment of the SB.

The DCB-BIF trial conducted by Gao et al.^[37] reports the results of a multicenter, randomized controlled trial comparing the use of a DCB versus a NCB to treat a stenosed SB after main-vessel stenting. Conducted across 22 centers in China, Indonesia, Italy, and Korea on 784 real-world bifurcation patients with $\geq 70\%$ side-branch stenosis after main-vessel stenting, patients were randomly assigned into two groups to receive either DCB (391 patients) or NCB (393 patients) in the SB. At the 1-year follow-up, the primary endpoint (MACE)—defined as a composite of cardiac death, target vessel myocardial infarction, or clinically driven TLR (re-opening of the vessel) – occurred in 7.2% of the DCB group and 12.5% of the NCB group, demonstrating a statistically significant reduction in favor of DCB (HR: 0.56; 95% CI: 0.35–0.88; $p=0.013$). This positive outcome was primarily driven by a reduction in periprocedural myocardial infarction rates; no significant difference was observed between the two groups regarding other major parameters such as procedural success, the need for crossover to a two-stent technique, all-cause mortality, or stent thrombosis. The study concluded that applying a DCB to a jailed SB during provisional stenting of simple and true bifurcation lesions markedly reduces the 1-year risk of adverse cardiac events compared to NCB, though caution should still be exercised against periprocedural early-phase heart attacks whose exact clinical significance remains to be fully elucidated.^[37]

In line with current ESC recommendations and the European Bifurcation Club consensus document, the use of a DCB in SB with appropriate lesion preparation and no flow-limiting dissection is recommended at a Class IIa (Level of Evidence B) level; this approach avoids the creation of a dual-layer metallic cage (sandwich effect) at the side-branch ostium and may improve acute procedural results. The available randomized evidence is nevertheless confined to angiographic endpoints and to follow-up of 1–2 years; in DCB-BIF the reduction in the composite endpoint was driven predominantly by periprocedural myocardial infarction, the prognostic significance of which remains debated. Claims of a reduction in late stent thrombosis or in long-term intra-bifurcation restenosis are not currently supported by outcome data.^[22,38]

Patients at HBR

In high-bleeding-risk patients – such as the elderly, those with chronic kidney disease, active bleeding, or those requiring mandatory oral anticoagulants – the use of dual antiplatelet therapy for 3–6 months (or longer) post-DES brings about fatal bleed-

ing risks. Because vessels treated with a DCB carry neither a permanent metallic cage nor a polymer, re-endothelialization is thought to proceed more rapidly. On this basis, consensus documents suggest that Dual antiplatelet treatment (DAPT) may be shortened to approximately 1 month after a DCB-only procedure, with still shorter durations considered when urgent surgery is required. It should be stressed that this guidance derives largely from expert opinion, registry data, and pathophysiological reasoning rather than from dedicated randomized trials of DAPT duration after DCB-only PCI.^[8]

ACS

In ACS scenarios such as Acute Myocardial Infarction (STEMI and NSTEMI), lesions are typically thrombus-laden, and vessel tone is prone to spasm. Stents deployed during this acute phase may turn out to be undersized once the vasospasm resolves (stent malapposition), which can lead to early or late stent thrombosis. A DCB-only strategy following thrombus aspiration and optimal predilation has been associated with late lumen enlargement in some angiographic series, although this observation derives from small studies and its clinical relevance is unproven. The REVELATION ($n=120$) and PEPCAD NSTEMI ($n=210$) randomized trials provide preliminary evidence that a DCB-based strategy is feasible in selected ACS patients and comparable to stenting over short-term follow-up.^[39,40] Both were modest in size and powered for surrogate or composite endpoints; neither establishes long-term safety, and DES implantation remains the guideline-recommended default strategy in ACS.

Use of DCB in CTO of Coronary Arteries

In CTO, DCBs have been explored as a means of limiting the length of implanted metal, which in this setting is frequently considerable. In lesions characterized by limited calcification, diffuse disease and a preserved distal vascular bed, a stent-free approach – or a hybrid approach in which the proximal segment is stented and the distal segment treated with a DCB – has yielded encouraging results for late lumen gain and vascular remodeling.^[41] This evidence, however, rests on a single systematic review and meta-analysis of predominantly observational and small randomized studies, with heterogeneous techniques and short follow-up. No adequately powered randomized trial has compared a DCB-based strategy with contemporary DES in CTO, and the present data should therefore be regarded as hypothesis-generating.

Future Perspectives, Limitations, and Conclusion

DCB technology is currently the principal clinically available expression of interventional cardiology's "leave nothing behind" paradigm. Nevertheless, the method possesses its own limitations. The greatest constraint lies in the potential occurrence of acute flow-limiting dissections (Type C-F) and elastic recoil following predilation. In such scenarios, bail-out stenting is mandatory before the patient leaves the catheterization laboratory. Bail-out rates are not trivial and must be factored into procedural planning: 9.4% of patients randomized to the DCB arm of

REC-CAGEFREE I required rescue stenting. DCB is therefore not a technology that will eliminate the stent, but a complementary strategy that removes the need for one in selected cases.^[8,34]

A second and closely related constraint is the extent to which outcomes depend on lesion preparation. Every favorable trial cited in this review mandated protocol-driven predilatation and enrolled patients at experienced, high-volume centers, and in several, the DCB was withheld unless pre-specified criteria for residual stenosis, flow, and dissection had been met. Results obtained under these conditions may not be reproducible in routine practice, where preparation is more variable and access to plaque-modification tools and intravascular imaging is uneven. The learning curve associated with DCB-only procedures is real but has not been formally quantified, and no trial has reported outcomes stratified by operator or center experience.

Evidence for the newer SCB remains considerably less mature than for paclitaxel-based platforms. The comparative data are dominated by non-inferiority designs with angiographic primary endpoints and modest sample sizes, such as SIBLINT-ISR and TRANSFORM I, supplemented by registry experience including the EASTBOURNE cohort, which lacks a randomized control arm. Because sirolimus is cytostatic and binds reversibly, its tissue-retention profile differs from that of paclitaxel, and it cannot be assumed that the longer-term durability established for paclitaxel-coated devices will be replicated. Outcome data beyond 2–3 years are largely lacking.

Several methodological limitations constrain the interpretation of the DCB literature as a whole. Late lumen loss and other angiographic surrogates remain the primary endpoint in the majority of trials, and no randomized study has been powered for mortality. Endpoint definitions have historically varied between studies, hindering pooling; the recent DCB Academic Research Consortium consensus is intended to address this, but its effect will be felt only in trials designed after its publication. Substantial evidence gaps persist in de novo disease outside the small-vessel setting, including large-vessel lesions, left main disease, multivessel disease and long diffuse lesions, for which randomized data are either absent or, as in REC-CAGEFREE I, do not support a DCB-first approach.

Two further considerations deserve mention. First, the excess late-mortality signal reported in a 2018 meta-analysis of paclitaxel-coated devices in the femoropopliteal circulation – although not reproduced in subsequent patient-level analyses or in coronary datasets, and no longer regarded as a barrier to use – illustrates how a literature built on surrogate endpoints may fail to detect safety signals that emerge only on long-term follow-up. Second, access remains uneven: DCBs are widely available in Europe and Asia, whereas in the United States a single device has been approved and, to date, only for ISR. Cost and reimbursement therefore continue to shape practice patterns independently of the evidence.

In summary, in addition to the solid clinical foundation established by paclitaxel-based platforms, the introduction of new-generation SCBs with nanotechnological carriers has broadened the range of lesions in which a DCB-based strategy

can reasonably be considered. Procedural success depends less on device selection than on meticulous and unhurried lesion preparation. Whether the role of DCBs in contemporary coronary intervention expands further will depend on the results of adequately powered randomized trials in de novo disease with clinical endpoints and prolonged follow-up, and on the development of lower-profile balloon designs. On present evidence, DCB is an established option in ISR and small-vessel disease, and an investigational one elsewhere.

Disclosures

Conflict of Interest Statement: There is no conflict of interest among the authors.

Funding: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: None declared.

Author Contributions: Concept – H.G., Ç.K.; Design – H.G., Ç.K., M.O.G.; Supervision – M.O.G.; Resource – H.G., Ç.K.; Materials – H.G.; Data collection and/or processing – H.G., Ç.K.; Data analysis and/or interpretation – H.G., M.O.G.; Literature search – H.G.; Writing – H.G., Ç.K.; Critical review – H.G., M.O.G.

Peer-review: Externally peer-reviewed.

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