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Review

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Narrative Review on "Sirolimus-Coated Balloons in Complex Percutaneous Coronary Intervention: Potential Implications for Chronic Total Occlusion Bifurcations"

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Abstract: Chronic total occlusions (CTOs) situated at or immediately adjacent to a coronary bifurcation represent one of the most technically and biologically demanding substrates encountered in percutaneous coronary intervention (PCI). The conventional "full metal jacket" strategy multiple, often overlapping drug-eluting stents carries a durable burden of stent thrombosis, neoatherosclerosis, side-branch jailing, and prolonged dual antiplatelet therapy (DAPT). This narrative review appraises the translational rationale for nanomaterial-engineered sirolimus-coated balloons (SCBs) as a metal-minimising strategy in complex percutaneous coronary intervention (PCI), with particular attention to the nanocarrier engineering that renders pharmacologically adequate sirolimus delivery achievable, and to its potential implications for the anatomically hostile CTO-bifurcation setting. The evidence base summarised here is predominantly observational and was not generated from a cohort specifically defined by CTO-bifurcation anatomy. Mechanistic, procedural, and registry-level evidence is synthesised, with emphasis on the phospholipid Nano carrier and crystalline matrix platforms that overcome sirolimus's comparatively modest lipophilicity relative to paclitaxel, thereby enabling near-instantaneous endothelial transfer and sustained antiproliferative elution—the bench-to-bedside translation that underpins the clinical data reviewed here. Across the FASICO, SIROOP, EASTBOURNE, and ERCTO registries, SCB-based strategies achieved procedural success rates of 96–100%, a 12-month major adverse cardiac event (MACE) rate as low as 4.3%, and a 2-year target lesion revascularisation (TLR) rate of 9% in large-vessel disease. Propensity-matched ERCTO data additionally demonstrated significantly shorter total stent length (44.2 mm vs. 58.1 mm) and a lower pericardial tamponade rate (0.1% vs. 0.4%) when a selective drug-coated balloon (DCB) strategy was employed. None of these four registries enrolled a dedicated, prospectively defined cohort of CTO bifurcation lesions; each captured broader complex-PCI or CTO-PCI populations in which bifurcation anatomy was represented but not separately analysed, and the figures above should therefore be read as indirect, overlapping-subset evidence rather than bifurcation-specific data. Phospholipid nanocarrier-based sirolimus delivery offers a biologically plausible route to effective antirestenotic therapy with substantially reduced permanent metallic scaffolding, and the indirect clinical signal reviewed here is consistent with that rationale, but it does not yet constitute direct proof of benefit in CTO bifurcations specifically. Randomised confirmation from the TRANSFORM-II trial, together with dedicated bifurcation-specific data, is required before this nanomedicine platform can be regarded as a default strategy in this setting.

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Keywords: chronic total occlusion; coronary bifurcation; sirolimus-coated balloon; drug-coated balloon; nanocarrier drug delivery; percutaneous coronary intervention

1. Introduction

CTOs located at or immediately proximal to a coronary bifurcation present a uniquely demanding convergence of mechanical and biological challenges. These lesions are typically long and heavily calcified, and they involve collateral and side-branch vasculature that is itself frequently diseased [1,2]. A true bifurcation lesion, in which disease involves the ostium of the side branch itself, carries different mechanical and procedural implications from a CTO that is simply located adjacent to an otherwise healthy bifurcation, a distinction conventionally captured by the Medina classification and related angiographic schemes [1,3]; this review uses the term "CTO bifurcation" to encompass both patterns unless a specific study defines the lesion more narrowly. Carina geometry amplifies the mechanical stress imposed on any scaffold deployed across the segment, and the differential tapering between the main vessel and its daughter branches compounds this effect further. Restenosis and re-occlusion rates in bifurcation CTOs have historically exceeded those observed in simpler, non-bifurcating lesions, and procedural risk is correspondingly elevated [2].

For nearly two decades, the default operative strategy has been the "full metal jacket" approach: multiple, frequently overlapping drug-eluting stents deployed to achieve complete coverage of the recanalised segment, often extending into one or both bifurcation limbs [1,2]. This strategy improved acute angiographic outcomes relative to bare-metal scaffolding or balloon angioplasty alone, but at the cost of a durable burden of late complications. Overlapping struts create zones of disturbed shear stress that predispose to neoatherosclerosis and delayed re-endothelialisation; cumulative metallic load raises the lifetime risk of stent thrombosis, particularly at strut-overlap and carina sites; permanent scaffolding abolishes physiological vasomotion; side-branch ostia are jailed by main-vessel struts; and the extensive stented length of a full-metal-jacket result often pushes antiplatelet decision-making toward the longer end of guideline-recommended dual antiplatelet therapy (DAPT) regimens, particularly where overlapping struts, bifurcation stenting, or high-risk anatomy are present [2,4].

These liabilities have driven interest in a "leave nothing behind" paradigm, realised clinically through drug-coated balloon (DCB) angioplasty [5]. A DCB delivers an antiproliferative agent directly to the arterial wall during balloon inflation and is then withdrawn, leaving native vessel architecture and its capacity for vasomotion and future revascularisation intact. Conceptually, this is as much a nanomedicine drug-delivery problem as it is an interventional one: the antiproliferative payload must be formulated and released so that it survives transit through the guide catheter and lesion, achieves near-instantaneous transfer upon balloon-wall contact, and then persists in the tissue long enough to suppress the neointimal proliferative response. It is precisely at this bench-to-bedside interface where formulation chemistry determines procedural feasibility that nanocarrier engineering becomes clinically decisive [6].

Early DCBs relied on paclitaxel, a highly lipophilic cytotoxic agent whose physicochemical properties made balloon coating comparatively straightforward [5]. Paclitaxel partitions readily into lipid-rich cell membranes, and simple excipients such as iopromide or urea are sufficient to facilitate rapid tissue transfer. Sirolimus poses a different translational problem. It is a cytostatic macrolide with considerably lower lipophilicity than paclitaxel, and its mechanism of action mTOR inhibition with G1-phase cell-cycle arrest is biologically more attractive, being associated with a lower-inflammation healing response than paclitaxel's direct cytotoxicity [7]. However, early attempts to apply sirolimus as a simple crystalline or amorphous balloon coating produced inconsistent, often inadequate tissue transfer within the brief inflation window available in a beating coronary artery a clear illustration of a favourable pharmacological rationale that could not, on its own, be translated into a workable device.

The solution has been one of nanomaterial engineering rather than pharmacology alone. Contemporary SCBs encapsulate sirolimus within sub-micron lipophilic carrier systems, phospholipid bilayer nanoparticles and crystalline nanocarrier matrices of the Nanolute type typically 100–300 nm in diameter [8]. This nanocarrier architecture serves two complementary translational functions. First, the phospholipid shell confers transient amphiphilicity on the drug, enabling membrane fusion and endocytosis by endothelial and medial smooth muscle cells within the 30–60 s balloon inflation window. Second, the same matrix acts as an intramural depot, protecting residual drug from coronary blood-flow washout and supporting sustained elution over approximately 8–12 weeks, broadly coincident with the proliferative phase of the vascular injury response [8]. These particle-size, uptake-window, and elution-duration figures derive from device-specific formulation and preclinical characterisation rather than from the clinical registries reviewed in Section 3, and they should be read as platform specifications rather than as directly clinically measured parameters. The nanocarrier platform provides the mechanistic rationale by which the drug is intended

to reach, and remain at, the target tissue, though the registries summarised later in this review were not designed to establish this mechanism as the direct cause of the clinical outcomes observed (Figure 1).

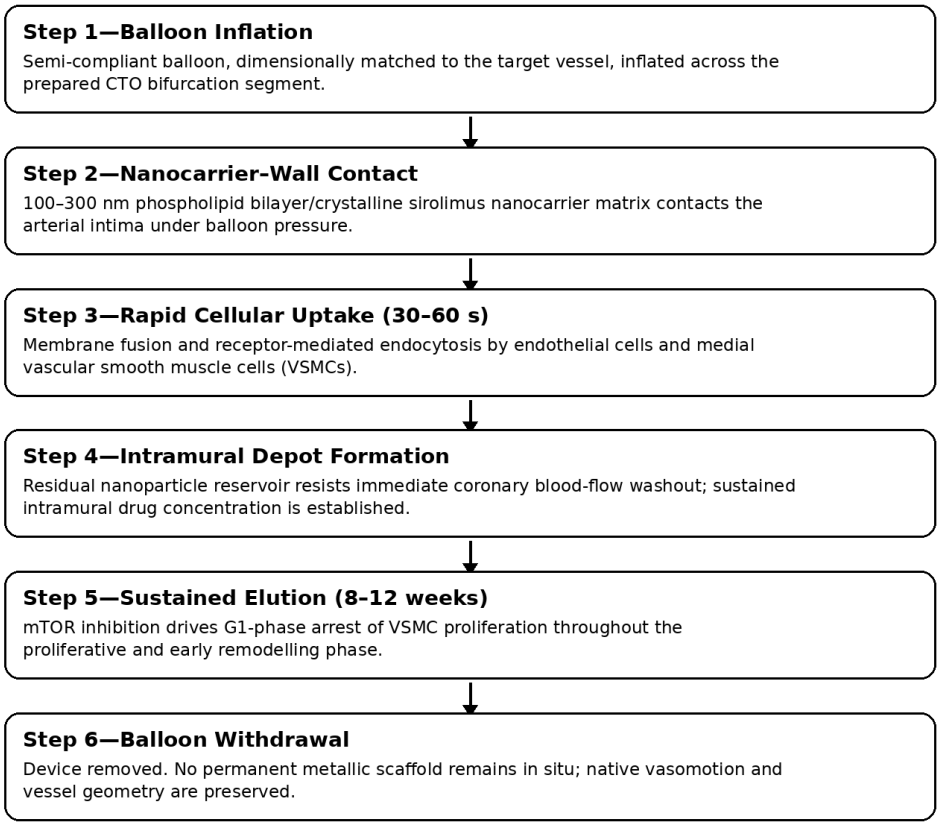

Figure 1. Nanoparticle drug-delivery mechanism of the sirolimus-coated balloon. Steps 1–6 illustrate the sequence from balloon inflation to sustained intramural elution following withdrawal of the device.

A scope caveat should be stated at the outset. The four registries appraised in Section 3 (FASICO, SIROOP, EASTBOURNE, and ERCTO) were designed around complex-PCI or CTO-PCI populations rather than a prospectively defined, dedicated bifurcation-CTO cohort, and none reports a bifurcation-specific analysis as a primary endpoint. This review therefore draws on the closest available evidence, complex- and CTO-PCI datasets in which bifurcation anatomy is represented but not isolated, and interprets it as indirect support for the CTO-bifurcation setting rather than as direct, dedicated proof. To keep this distinction explicit throughout, Section 3 classifies the cited evidence into three tiers: direct evidence from studies specifically addressing CTO bifurcations, supportive evidence from CTO-PCI studies without a separate bifurcation analysis, and indirect evidence from complex-PCI or large-vessel SCB studies without a CTO-specific focus.

This review synthesises the mechanistic rationale, procedural strategy, and accumulated registry-level clinical evidence for nanocarrier-formulated SCBs in complex PCI, and considers the potential implications of this evidence for CTO bifurcations specifically, an anatomical setting in which minimising permanent metallic scaffolding while preserving geometry and procedural safety would be of particular value.

2. Materials and Methods: Clinical Concepts and Engineering Matrix

2.1. Literature Search and Selection Methodology

This is a narrative rather than a systematic review; a formal PRISMA-type protocol was not registered, and the search below was designed for breadth of mechanistic and clinical coverage rather than exhaustive retrieval. Literature was identified through structured searches of PubMed/MEDLINE and Embase, supplemented by manual screening of EuroIntervention, Catheterization and Cardiovascular Interventions, and reference lists of retrieved articles for registry and trial records not captured by the primary search. Search terms combined “sirolimus-coated balloon”, “drug-coated balloon”, “chronic total occlusion”, “coronary bifurcation”, “nanocarrier”, and “percutaneous coronary intervention”, with Boolean operators.

Records were considered for inclusion if they reported registry-level, cohort, or randomised clinical data on sirolimus- or paclitaxel-coated balloon use in complex coronary anatomy, including CTO or bifurcation lesions,

or if they described the pharmacology and nanocarrier engineering underlying SCB drug delivery. Case reports, non-peer-reviewed abstracts, and studies not reporting procedural or clinical outcomes were excluded. Title/abstract screening and full-text selection were performed by the corresponding author, with the final reference list reviewed and agreed by all co-authors. Four registries (FASICO, SIROOP, EASTBOURNE, and ERCTO) met the inclusion criteria and clinical relevance threshold to serve as the primary evidence base for Section 3; supporting mechanistic, procedural, and comparator references are cited throughout the text. As detailed in Section 1, none of the included registries isolates a bifurcation-specific CTO subgroup, and this limitation is carried forward into the synthesis and limitations discussed in Sections 3.5 and 3.6. [Authors should confirm the exact databases searched, the search date range, and the screening arrangement against their actual review process before resubmission].

2.2. Structural Components of the SCB Nanomedicine Platform

A modern SCB system comprises three interdependent structural components, each essential to the clinical performance described in subsequent sections and each representing a distinct point at which bench-level engineering determines bedside outcome.

Component 1: The Delivery Catheter. A semi-compliant balloon catheter, dimensionally matched to the target vessel and designed for low-profile crossing through the calcified, tortuous segments typical of recanalised CTOs. Semi-compliance permits adequate wall apposition for nanoparticle transfer without the excessive radial force of non-compliant balloons, which are reserved for the preparatory phase rather than drug delivery.

Component 2: The Antiproliferative Payload. Sirolimus inhibits mTOR, arresting vascular smooth muscle cell (VSMC) proliferation in the G1 phase of the cell cycle. This cytostatic mechanism is mechanistically distinct from, and biologically gentler than, paclitaxel's cytotoxic microtubule-stabilising action, producing an antirestenotic effect without direct cellular toxicity.

Component 3: The Nanocarrier Matrix. Sirolimus is not applied in free crystalline form but is embedded within a crystalline phospholipid nanocarrier matrix, the Nanolute-type formulation comprising nanospheres in the 100–300 nm range [8]. This matrix constitutes the engineering solution to sirolimus's inadequate native lipophilicity. It determines the kinetics of tissue transfer and retention described in Section 1 and, consequently, the clinical outcomes discussed in Section 3, forming the direct mechanistic link between nanomaterial design and clinical efficacy.

2.3. Procedural Strategy for the CTO Bifurcation

Successful deployment of SCB technology in a CTO bifurcation depends on a strict, sequential procedural algorithm; drug-coated balloon therapy performs no better than the luminal preparation that precedes it [9,10] (Figure 2).

The occluded segment is first traversed using standard antegrade wire-escalation or, where antegrade approaches fail or are anatomically disadvantaged, retrograde techniques via collateral or epicardial channels, in accordance with established hybrid CTO algorithms [2].

Lesion crossing is the non-negotiable prerequisite for any DCB-only strategy. Predilation is then performed using non-compliant balloons, scoring or cutting balloons, or, where calcification is severe, adjunctive calcium-modification devices. The procedural target is a residual diameter stenosis below 30% and an angiographic result free of flow-limiting or type C–F dissection before any SCB is introduced. Intravascular imaging (IVUS or OCT), where available, adds meaningful information at this stage: it allows more accurate vessel sizing than angiography alone, characterises the extent and distribution of calcification, and helps confirm that luminal gain is adequate before the operator commits to a DCB-only strategy rather than bailout stenting [11]. Severe, particularly circumferential, calcification is common in recanalised CTO segments and is often the limiting factor in achieving adequate preparation; where standard non-compliant, scoring, or cutting balloons fail to modify it, adjunctive calcium-modification techniques (for example intravascular lithotripsy or rotational or orbital atherectomy) should be considered before SCB deployment is attempted [12]. Inadequate preparation is the single most consequential determinant of DCB failure: an under-prepared vessel both impairs nanoparticle-to-wall contact and predisposes to acute recoil or dissection that the device cannot scaffold [10]. Other recognised predictors of DCB failure include suboptimal distal runoff, major (type C or greater) dissection following predilation, and vessel recoil disproportionate to the preparation achieved; any of these should prompt a low threshold for bailout stenting rather than proceeding with drug delivery to a compromised segment.

Once preparation criteria are met, SCBs are applied according to a provisional or dual-balloon strategy tailored to bifurcation geometry. In the provisional approach, the main vessel is treated with a single SCB inflation

sized to the parent vessel, with the side branch managed conservatively unless compromised. Where both limbs require treatment, sequential or near-simultaneous dual-balloon SCB inflations are performed, mirroring kissing-balloon technique but substituting permanent scaffolding with nanocarrier-mediated drug transfer. Metallic implantation is reserved for focal bail-out scenarios, flow-limiting dissection, recoil, or perforation [9,13].

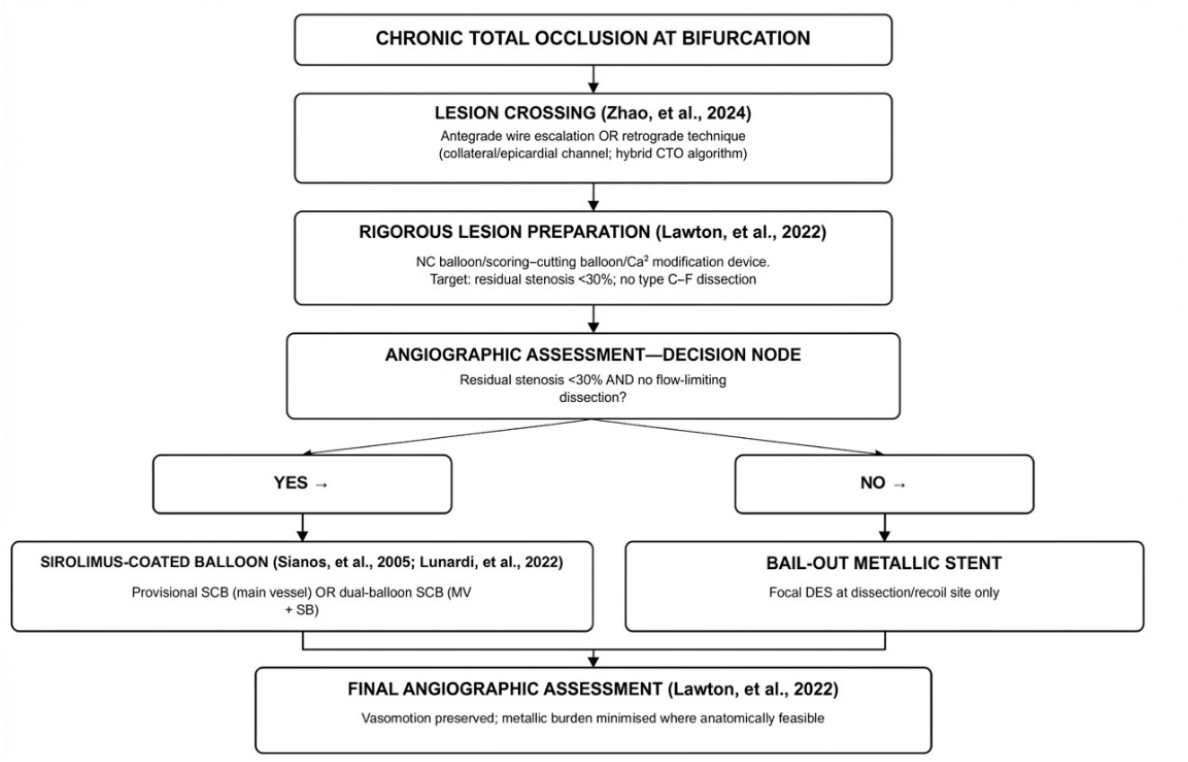

Figure 2. Procedural decision algorithm for CTO bifurcation management with selective SCB strategy. Bail-out metallic stenting is reserved for focal dissection or recoil unresponsive to prolonged balloon inflation [1,3,4,6].

3. Results and Discussion: Synthesis of Clinical Evidence

3.1. Early Procedural Safety: The FASICO Registry

The FASICO (FAtebenefratelli SIrolimus COated-balloon) registry provided one of the earliest dedicated real-world assessments of a first-generation SCB platform in genuinely complex anatomical substrates, enrolling 32 patients across 34 complex lesions [9]. Procedural success was achieved in 100% of cases, with no acute stent thrombosis and no late vessel closure. The modest sample size limits statistical power and precludes definitive safety conclusions; this is appropriately contextualised by FASICO's proof-of-concept design, which aimed to establish that a sirolimus nanocarrier formulation could be deployed safely and effectively in precisely the anatomically hostile lesions for which the technology was ultimately intended [9]. At a time when DCB experience was almost entirely paclitaxel-based, this was the necessary first demonstration that nanocarrier engineering could translate into acceptable acute procedural behaviour outside a first-in-human trial.

3.2. Contemporary Crystalline Sirolimus Performance: The SIROOP Registry

SIROOP extended this evidence considerably, enrolling 126 all-comer patients treated with a contemporary crystalline sirolimus DCB between 2021 and 2023 [8]. The risk profile was substantial: nearly half of patients presented with an acute coronary syndrome, approximately one-third had high-grade calcification, and eleven patients carried a true CTO. Despite this, the registry recorded 100% procedural success and a MACE rate of only 4.3% at twelve months [8]. The combination of an unselected, comorbidity-laden population and a favourable composite event rate is clinically meaningful: it suggests that crystalline sirolimus nanocarrier formulations have matured substantially since the FASICO era, and that the biological rationale of a cytostatic, lower-inflammation payload is translating into measurable benefit rather than remaining a theoretical construct.

3.3. Large-Vessel, Multicentre Confirmation: The EASTBOURNE Registry

EASTBOURNE is, by a considerable margin, the largest real-world dataset for SCB therapy, encompassing 2440 lesions across 2123 patients treated at multiple centres [13]. Acute procedural success was 96%, and the two-year TLR rate in large coronary vessels was 9% [13]. The scale of this registry is important: a 9% two-year TLR in an unselected, multicentre, large-vessel population is consistent with durable antirestenotic efficacy, and the sample size substantially reduces the likelihood that the favourable outcomes observed in FASICO and SIROOP reflect single-centre expertise or patient selection rather than a reproducible treatment effect.

3.4. Selective DCB Strategy in the True CTO Population: The ERCTO Registry

The European Registry of Chronic Total Occlusion (ERCTO), drawing on 40,000 CTO-PCI procedures performed between 2016 and 2023, provides the largest available dataset on DCB use within a true-CTO population [10]. It should be noted that ERCTO captures drug-coated balloon use broadly, encompassing both sirolimus- and paclitaxel-coated devices, rather than SCB use specifically; it therefore constitutes supportive rather than SCB-specific evidence, and, like the other three registries, it does not isolate a dedicated bifurcation subgroup for separate analysis. DCB use in side branches or distal vessel segments rose from 6.2% to 15% over the study period, a trend documenting a genuine shift in operator practice toward selective metal-sparing strategies in precisely the bifurcation and distal-vessel scenarios most germane to this review; a recent meta-analysis focused specifically on bifurcation side-branch treatment similarly reports growing, though still limited, evidence for DCB use at this location [14,15]. Propensity-matched analysis showed that a selective DCB strategy was associated with a significantly shorter total stent length (44.2 mm vs. 58.1 mm) and a significantly lower rate of pericardial tamponade (0.1% vs. 0.4%) relative to a stent-only approach [10]. (Figure 3, Table 1).

Table 1. Clinical evidence matrix for SCBs in complex PCI.

Registry	Period	n	Population	Safety Outcome	Efficacy Outcome	Ref.
FASICO	Early cohort	32 pts/34 lesions	Complex PCI; heavily calcified substrates	100% procedural success; no acute ST; no late closure	Proof-of-concept for first-generation SCB platform	[9]
SIROOP	2021–2023	126 pts (all-comers)	~50% ACS; ~33% calcification; 11 true CTOs	100% procedural success	4.3% MACE at 12 months	[8]
EASTBOURNE	Multicentre	2123 pts/2440 lesions	Large-vessel disease (predominantly)	96% acute procedural success	9% TLR at 2 years	[13]
ERCTO	2016–2023	40,000 CTO-PCI	True CTOs	Tamponade: 0.1% (DCB) vs. 0.4% (stent-only) *	Stent length: 44.2 mm vs. 58.1 mm *; DCB use 6.2% → 15%	[10]

ACS = acute coronary syndrome; MACE = major adverse cardiac events; ST = stent thrombosis; TLR = target lesion revascularisation. * Propensity-matched comparison (ERCTO).

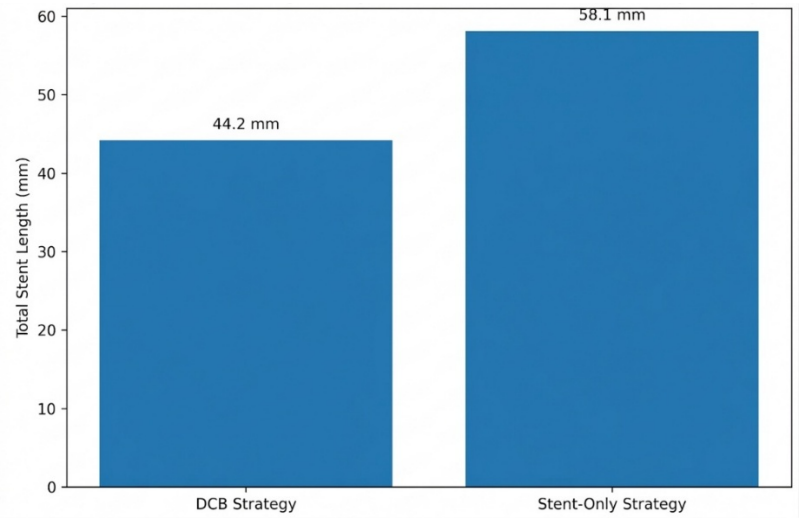

Figure 3. Total stent length comparison between DCB and stent-only strategies in propensity-matched ERCTO cohorts. A reduction of 13.9 mm was observed alongside a lower rate of pericardial tamponade; this association is

hypothesis-generating and does not establish a causal mechanism. Data from Ciardetti et al., 2025 [10]. Difference in stent length: −13.9 mm (DCB vs. Stent-Only), $p < 0.001$. Tamponade rate reduction: 0.4%→0.1% (statistically significant). Data: Ciardetti et al., 2025 [10].

The tamponade finding warrants particular attention, but its interpretation should be treated with caution. Tamponade in CTO-PCI is multifactorial, encompassing wire perforation, balloon oversizing, and collateral-channel trauma among other mechanisms, and the propensity-matched design cannot exclude residual confounding or establish a direct causal pathway between metallic burden and this specific complication. A reduction in cumulative metallic and mechanical burden on a recanalised, often friable CTO segment is one plausible contributor, but this remains a hypothesis generated by the observational association rather than a demonstrated mechanism, and it is presented here as such pending prospective evaluation.

3.5. Comparative Pharmacology and the Path to Randomised Confirmation

Taken together, these four registries build a progressively broader, though still indirect, body of evidence: early demonstration of acute safety in complex anatomy (FASICO [9]), confirmation of efficacy in a contemporary high-risk all-comer population (SIROOP [8]), large-scale multicentre validation of mid-term durability (EASTBOURNE [13]), and, within the true CTO population, an association between a selective DCB strategy and reduced metallic burden alongside a lower rate of a major procedural complication (ERCTO [10]). The nanocarrier-mediated delivery platform underlies the mechanistic rationale common to all four datasets, and the pattern of favourable outcomes is consistent with that rationale; however, the registries were not designed to isolate the nanocarrier formulation as the cause of the clinical results observed, and the association should be read as supportive rather than as proof that the formulation chemistry itself drives the outcomes. (Table 2).

Table 2. Balloon/drug technology and CTO-bifurcation evidence-tier classification for the four principal registries. * Evidence tiers: Direct—dedicated CTO-bifurcation cohort with a bifurcation-specific analysis; Supportive—CTO-PCI study without a separate bifurcation analysis; Indirect—complex-PCI or large-vessel SCB study without a CTO-specific focus. No registry included here meets the Direct tier.

Registry	Balloon Technology/Coating	CTO Proportion	Bifurcation-Specific Analysis?	Evidence Tier*	Ref.
FASICO	Sirolimus-coated, crystalline nanocarrier (first-generation platform)	0/32 (not a CTO-specific cohort)	No	Indirect	[9]
SIROOP	Sirolimus-coated, crystalline nanocarrier	11/126 true CTO (8.7%)	No	Supportive (CTO subset only)	[8]
EASTBOURNE	Sirolimus-coated, phospholipid/crystalline nanocarrier	Not reported (large-vessel population)	No	Indirect	[13]
ERCTO	Mixed DCB use—sirolimus- and paclitaxel-coated devices	40,000/40,000 (100% CTO-PCI)	No (side-branch/distal-vessel use analysed; no isolated bifurcation cohort)	Supportive	[10]

The pharmacological comparison with paclitaxel remains relevant context, though it should be read as platform- and setting-dependent rather than as a general claim of biological superiority. Paclitaxel achieves rapid antiproliferative effect through direct cytotoxicity but has been associated in some settings with delayed healing and a less favourable late inflammatory profile, as reflected in longer-term BASKET-SMALL 2 data [5]; the magnitude of this difference depends on the specific balloon platform, excipient, drug dose, and coating technology under comparison, and head-to-head data specific to the CTO-bifurcation setting are not available. Sirolimus's cytostatic G1-phase arrest is mechanistically distinct, and the registry data reviewed above are broadly consistent with a favourable inflammatory profile, but this remains a plausible mechanistic explanation rather than one established by the cited registries themselves. Registry evidence, however large and consistent, cannot substitute for a randomised comparison. The TRANSFORM-II trial [16], which has completed patient enrolment with results awaited at the time of writing, was designed to test whether the favourable signal observed across these registries holds under randomised, controlled conditions; it does not itself enrol a dedicated CTO-bifurcation cohort, so its findings will still need to be extrapolated to this specific anatomical setting. (Table 3).

Table 3. Comparative pharmacology of sirolimus-coated vs. paclitaxel-coated balloon. Comparisons of inflammatory profile and elution duration reflect the general pharmacological rationale and preclinical/formulation-level data rather than a head-to-head clinical comparison; the magnitude and direction of any difference may vary with the specific balloon platform, excipient, and coating technology.

Parameter	Sirolimus-Coated Balloon	Paclitaxel-Coated Balloon
Mechanism	Cytostatic—mTOR inhibition, G1-phase VSMC arrest	Cytotoxic—microtubule stabilisation
Lipophilicity	Moderate (requires nanocarrier engineering)	High (direct membrane partitioning)
Nanocarrier required?	Yes—phospholipid bilayer/crystalline matrix	Excipient (iopromide/urea) sufficient
Tissue transfer window	30–60 s (nanocarrier-mediated endocytosis)	30–60 s (direct membrane partitioning)
Sustained elution	Approx. 8–12 weeks in preclinical/formulation data (intramural depot formation); platform-dependent	Days in preclinical/formulation data (rapid clearance after initial uptake); platform-dependent
Inflammatory profile	Theoretically lower (cytostatic, endothelium-preserving)	Theoretically higher (direct cytotoxicity)
Coating particle size	100–300 nm phospholipid nanoparticles	Crystalline/amorphous particulate
Key evidence	FASICO [9], SIROOP [8], EASTBOURNE [13], ERCTO [10]	BASKET-SMALL 2 [5]; multiple RCTs

3.6. Limitations of the Current Evidence Base

The evidence synthesised across Sections 3.1–3.5 must be interpreted within the constraints inherent to its observational design. None of the four registries included a pre-specified randomised comparator arm; consequently, outcomes reflect the combined influence of patient selection, centre expertise, operator experience, and device-generation effects that propensity matching can attenuate but cannot fully eliminate. The definition of procedural success, the composition of MACE endpoints, and the duration of angiographic and clinical follow-up differ across FASICO, SIROOP, EASTBOURNE, and ERCTO, limiting direct cross-registry comparison. Bailout-stenting rates and their predictors were not uniformly reported across the four datasets, which limits any quantitative synthesis of DCB-only failure and should be addressed explicitly in future registry and trial reporting.

The modest enrolment of FASICO (n = 32) and the eleven-patient CTO subgroup within SIROOP are insufficient to support subgroup-level statistical inference; their contribution is hypothesis-generating rather than confirmatory. The ERCTO propensity-matched analysis, while drawn from a large denominator of 40,000 procedures, is subject to unmeasured confounders including temporal trends in operator skill, catheter-laboratory technology, and adjunctive pharmacotherapy across the 2016–2023 study period. Publication bias toward positive outcomes in early-phase, single-centre registries cannot be excluded. These limitations do not invalidate the consistent signal observed across the four datasets, but they do underscore the necessity of the randomised evidence that the TRANSFORM-II trial [16] is designed to provide.

Several further limitations bear specifically on the CTO-bifurcation question this review sets out to address. First, no randomised clinical trial has yet addressed CTO bifurcation lesions as a dedicated cohort; TRANSFORM-II and the four registries reviewed here evaluate complex- or CTO-PCI populations in which bifurcation anatomy is present but not separately randomised or powered, so conclusions specific to bifurcation CTOs remain inferential rather than direct. Second, the SCB platforms underlying FASICO, SIROOP, EASTBOURNE, and ERCTO are not identical: phospholipid bilayer and crystalline nanocarrier formulations differ between manufacturers in particle size, coating density, and elution kinetics, and this platform- and manufacturer-level heterogeneity limits the extent to which findings from one device can be generalised to sirolimus-coated balloons as a class. Third, because treatment allocation was not randomised in any of the four registries, operators selectively directed SCB therapy toward lesions and patients judged anatomically and clinically suitable; this potential for selection bias means that the favourable outcomes reported may partly reflect case selection rather than treatment effect alone, a limitation that propensity matching in ERCTO can reduce but not eliminate. Finally, all four registries were conducted at experienced, high-volume centres with operators skilled in complex CTO and bifurcation technique, and the reproducibility of these outcomes in lower-volume or less-specialised centres has not been established.

4. Conclusions

Nanocarrier-formulated sirolimus-coated balloons represent a biologically plausible, metal-minimising alternative to full-metal-jacket stenting in complex PCI, with potential extension to CTO and bifurcation-adjacent anatomy, made possible by phospholipid bilayer and crystalline nanocarrier engineering that compensates for sirolimus's modest native lipophilicity and allows near-instantaneous tissue transfer during a brief balloon inflation, followed by sustained multi-week elution. This plausibility is supported by indirect and observational registry evidence rather than by data derived from a dedicated CTO-bifurcation study design.

Three take-home points follow. First, across the complex- and CTO-PCI registries appraised here, SCB-based strategies have consistently shown high procedural success, favourable mid-term event rates, and reduced cumulative metallic burden relative to stent-only approaches. Second, this evidence remains indirect with respect to CTO bifurcation lesions specifically, since no registry or randomised trial to date has isolated a dedicated bifurcation-CTO cohort; the case for SCB therapy in this precise anatomical subset is therefore presently inferential rather than confirmatory. Third, rigorous lesion preparation remains the non-negotiable precondition for any DCB-only strategy, and bail-out metallic scaffolding remains necessary when preparation or angiographic safety criteria are not met.

Until dedicated randomised evidence becomes available, nanocarrier-based SCB therapy in CTO bifurcations should be regarded as a selective, operator-judgement-dependent strategy rather than a default approach, adopted when lesion preparation and anatomy are suitable, and with the understanding that current supporting data are extrapolated from broader complex-PCI and CTO-PCI populations rather than derived from a bifurcation-specific study design.

Author Contributions

S.S.S.: conceptualization, methodology, literature search, screening, data curation, synthesis, writing original draft preparation, writing review and editing; S.A.: literature review, data curation, writing original draft, synthesis, writing review and editing; A.U.R.: literature review, screening, data curation, writing review and editing; Z.: literature review, data curation, writing review and editing. All authors have read and agreed to the published version of the manuscript.

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Data are contained within the article.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT for grammar correction only. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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