Drug-Coated Balloons

Applications in Interventional Cardiology

Bernardo Cortese
Editor

Second Edition

DCB INTERNATIONAL ACADEMY

Fondazione Ricerca e Innovazione Cardiovascolare

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Again and again to my travel companions, my beloved sons Luigino and Gu.

“Not all those who wander are lost”

—J.R.R. Tolkien

Preface

Drug-coated balloons (DCB) have become an important therapeutic option in interventional cardiology, particularly in situations where permanent metallic implantation is undesirable. Their ability to deliver antiproliferative therapy without leaving a scaffold behind has addressed several limitations associated with stent-based strategies, especially in the long term. As device technology and clinical experience have evolved, the use of DCB has expanded across a wide range of coronary and peripheral vascular indications.

This second edition of Drug-Coated Balloons: Applications in Interventional Cardiology provides an updated overview of the scientific basis, technical developments, and clinical applications of DCB therapy. The early chapters focus on the mechanisms of restenosis, principles of local drug delivery, and preclinical evaluation of paclitaxel- and limus-based technologies. Subsequent chapters address procedural aspects, including lesion preparation, intravascular imaging, physiology, complex lesion management, and post-intervention assessment.

The clinical sections explore the role of DCB across a broad spectrum of coronary scenarios, including in-stent restenosis, small-vessel disease, bifurcation lesions, calcific lesions, chronic total occlusions, and blended approaches combining DCB with drug-eluting stents. Dedicated chapters examine post-procedural dissections, late lumen enlargement, and long-term follow-up data derived from randomized controlled trials and real-world registries. Subsequent sections address procedural considerations that are central to a successful DCB angioplasty, with particular emphasis on lesion preparation, plaque modification strategies, intravascular imaging, and physiologic assessment. These chapters reflect the growing recognition that optimal vessel preparation and mechanism-based treatment are critical determinants of durable clinical outcomes following DCB use.

The application of DCB therapy in peripheral arterial disease, arteriovenous access dysfunction, and other vascular territories is also discussed, highlighting both shared principles and territory-specific considerations. The final sections of the book address antithrombotic strategies, reimbursement and cost-effectiveness, and current technical challenges that continue to shape the evolution of DCB therapy. Together, these chapters offer a balanced discussion of established evidence and areas of ongoing investigation.

This Book is intended for interventional cardiologists, fellows-in-training, and researchers seeking a practical and evidence-based reference on DCB therapy. By integrating mechanistic insights, experimental data, and clinical

experience, this book aims to support informed decision-making and thoughtful application of DCB technology in modern revascularization practice.

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I wish to thank Dr Irfan Ullah, my Research Fellow, who put passion and competence into supporting this project in the most delicate phases of its life.

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Milano, Milano, Italy Bernardo Cortese

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How New Technologies Can Overcome Stent Limitations

1

Dario Buccheri, Giulia Mingoia, and Bernardo Cortese

Abbreviations

ACS	Acute coronary syndromes
BENESTENT	Belgium Netherlands Stent Arterial Revascularization Therapies Study BMS Bare-metal stents
BVS	Bioresorbable vascular scaffold(s)
CAD	Coronary artery disease
DCB	Drug-coated balloon(s)
DEB	Drug-eluting balloon(s)
DES	Drug-eluting stent(s)
EES	Everolimus-eluting stent(s)
HBR	High bleeding risk
ISR	In-stent restenosis
MI	Myocardial infarction
NNT	Number needed to treat
PCI	Percutaneous coronary intervention
POBA	Plain old balloon angioplasty
PTCA	Percutaneous transluminal coronary angioplasty
ST	Stent thrombosis
STRESS	North American Stent Restenosis Study
TLR	Target lesion revascularisation
TVMI	Target vessel myocardial infarction

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1.1 Introduction: The Evolution of Coronary Revascularization

Over the last four decades, percutaneous coronary intervention (PCI) has evolved dramatically from a rudimentary mechanical approach into a sophisticated set of techniques and devices designed to optimize coronary flow, drastically reduce neointimal proliferation, and improve long-term clinical outcomes. It is now an established treatment option for patients with advanced coronary artery disease (CAD) [1].

The first percutaneous transluminal coronary angioplasty (PTCA), performed by Andreas Grüntzig in 1977, marked the beginning of catheter-based coronary revascularization [2]. Early treatments relied on plain old balloon angioplasty (POBA), which allowed vessel dilation but was limited by elastic recoil, flow-limiting dissections, and restenosis rates of 30–50% within the first year [3].

The introduction of bare-metal stents (BMS) in the late 1980s addressed many of these mechanical limitations. BMS provided permanent scaffolding, reduced recoil and abrupt vessel closure, and lowered restenosis rates compared with POBA, as demonstrated in landmark trials such as BENESTENT and STRESS [4]. Within just a few years in the early 1990s, stenting

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became the default procedure, heralding the era of "stent-o-mania" [5]. By 1999, stents were used in more than 80% of PCIs [3]. Nevertheless, BMS maintained restenosis rates of ~20–30%, driven primarily by neointimal hyperplasia [6].

1.1.1 Drug-Eluting Stents: A Major Technological Breakthrough

Drug-eluting stents (DES) emerged in the early 2000s as a response to BMS-associated restenosis. They consist of three components: a metallic stent backbone, an antiproliferative agent, and a drug carrier (usually a polymer coating). Until recently, two types of DES were widely available: sirolimus-eluting and paclitaxel-eluting stents. These effectively inhibited the neointimal hyperplastic response to vessel injury, achieving ~70% relative reductions in restenosis and target lesion revascularization (TLR), as conclusively demonstrated in RAVEL, SIRIUS, TAXUS-IV, and several meta-analyses. The number needed to treat to prevent one repeat revascularization was as low as 7–8 [6–9]. For a time, it appeared that the Achilles heel of stenting—restenosis had finally been conquered [10].

However, in 2006, during presentations at the European Society of Cardiology meeting, concerns emerged regarding the long-term safety of first-generation DES. Systematic reviews and meta-analyses showed that early generation CYPHER (sirolimus-eluting) and TAXUS (paclitaxel-eluting) stents were associated with a small but steady risk of late stent thrombosis (ST) beyond 1 year, compared with BMS (1.3% vs 0.8% for paclitaxel-eluting and 1.2% vs 0.6% for sirolimus-eluting stents) [11–13]. Their antiproliferative drugs markedly inhibited or delayed endothelialization of stent struts, rendering them more thrombogenic [14, 15]. These findings led to widespread adoption of prolonged dual antiplatelet therapy (DAPT) to mitigate late ST risk.

Second- and third-generation DES markedly improved safety through biocompatible polymers, thinner struts, and refined drug-release kinetics. Long-term follow-up from real-world registries and randomized trials now shows very low rates of late ST (<0.2%/year) and further reductions in restenosis [16–19]. DES currently represent the standard of care for most obstructive coronary lesions [20].

1.1.2 Limitations of Current Stent Technologies

Despite significant progress, DES retain intrinsic limitations due to the permanent presence of metallic scaffolds and polymer carriers, producing several mechanical, biological, and clinical challenges.

Mechanical Limitations [21]

- Loss of vasomotion: metallic stents permanently "cage" the vessel.
- Impaired vascular remodeling.
- Obstruction of distal access and side branches.
- Cumulative metal layers increase procedural complexity during re-intervention.

Biological Limitations [22]

- Chronic inflammation induced by metal and polymers.
- Neoatherosclerosis, beginning as early as 1–3 years post-PCI.
- Delayed healing despite newer-generation DES.

Clinical Limitations

- In-stent restenosis (ISR) and late ST remain relevant, and never stop.
- Prolonged DAPT is required, increasing bleeding risk in some patients subsets.

Intermediate- and long-term stent failure due to neointimal hyperplasia, neoatherosclerosis, or stent fracture still occurs. Consequently, there is growing interest in revascularization strategies that maintain vessel patency without a permanent scaffold.

1.1.3 The "Leave Nothing Behind" Paradigm

As it became clear that permanent scaffolds inherently limit vessel physiology, interventional cardiology progressively embraced the "leave nothing behind" concept—delivering potent antiproliferative therapy without permanent foreign material.The most ambitious attempt was the bioresorbable vascular scaffold (BVS). The ABSORB BVS (Abbott Vascular), composed of poly-L-lactic acid (PLLA), provided temporary mechanical support with resorption over 3 years, theoretically restoring vasomotor function and preventing late neoatherosclerosis.

Early randomized trials showed noninferiority to metallic DES in selected lesions, however, ABSORB II, III, and IV later demonstrated higher rates of scaffold thrombosis, target lesion failure, and target-vessel MI, especially within the first 3 years [23–29].

The failure of first-generation BVS highlighted two key lessons:

1. Transient scaffolding is insufficient if strut thickness, radial strength, and degradation kinetics are suboptimal.
2. Mechanical solutions alone cannot overcome the biological challenges of foreign implants.

This led to interest in non-scaffold technologies providing antiproliferative therapy while preserving vessel architecture—creating the basis for the rationale of drug-coated balloons use (DCB) [30–32].

1.1.4 Drug-Coated Balloons: A Paradigm Shift

DCB offer short-term intracoronary drug delivery without implantation of permanent hardware.

Mechanism of Action

DCB feature a semi-compliant balloon coated with a highly lipophilic antiproliferative drug—traditionally paclitaxel, more recently limus-based agents—embedded within an excipient that facilitates rapid transfer during inflation [33].

Key principles:

- Very high local drug concentrations.
- Brief delivery (30–60 s).
- Tissue retention enabling weeks of antiproliferative activity.
- No polymer or metal, eliminating chronic inflammatory stimuli.

Despite only part of the drug being transferred (this portion is variable between <10 and 30% for most of the available devices), this is sufficient to immediately suppress neointimal proliferation and, later, promote positive remodeling [33, 34].

Clinical Rationale

DCB were initially designed for ISR, where additional metal is undesirable [35]. Their advantages include:

- Preserved vasomotion.
- Avoidance of multiple metal layers.
- Potential for shorter DAPT.
- Maintained side-branch access.

They may also be used in lesions where DES cannot be delivered or perform poorly, such as tortuous vessels, small vessels, long diffuse lesions, calcified segments at risk of stent fracture, or bifurcation lesions [21, 36, 37].

Technology Diversification

- Paclitaxel-coated balloons are the most established ones.
- Sirolimus-coated balloons and nanoparticle-based delivery systems are emerging due to their cytostatic profile.

The field of DCB innovation is rapidly expanding and will be explored in details in the next Chapters.

1.1.5 Beyond DCB–Emerging Technologies and Future Directions

Current research explores several complementary developments:

- Nanotechnology-based drug-delivery platforms improving transfer efficiency [36, 37].
- Optimized lesion preparation.
- Hybrid strategies combining DES and DCB [38].
- Expanding indications beyond coronary disease, including peripheral ISR, SFA, BTK interventions, AV fistulae, and erectile dysfunction.
- Advanced intravascular imaging and physiology to guide DCB use and assess outcomes [39, 40].

DCB are increasingly viewed not merely as an alternative to DES but as part of a broader strategy to restore arterial biology while minimizing device-related complications.

1.1.6 Conclusion

Coronary stent technology has transformed interventional cardiology, yet permanent implants have intrinsic limitations. Emerging technologies, particularly DCB, represent a shift toward temporary, targeted, and biologically compatible therapy [41]. Restoring vascular function, rather than simply repairing it, is the next frontier. This book was designed to better understand how this technology is working, and how it will be able to change our approach to coronary artery disease. In the next chapters we will go into the details of this new frontier of Interventional Cardiology.

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2 Drug-Coated Balloons: Local Drug Delivery to Prevent Restenosis of Coronary and Peripheral Arteries—Basic Principles

Andre M. Nicolau, Carlos M. Campos, Hernan Patricio G. Meija, and Alexandre Abizaid

2.1 Introduction

Despite advances in stent design and drug therapy, stent thrombosis occurs at a rate of approximately 0.1% annually, while in-stent restenosis (ISR) requiring revascularization remains at 0.5–1.0% per year, with minimal reduction up to 10 years after PCI and higher rates in more complex lesion settings [1]. Metallic scaffolds can impair vessel remodeling and pulsatility, hindering positive adaptive changes and potentially triggering chronic inflammation and neoatherosclerosis. The stent's presence disrupts normal vessel biomechanics and cell signaling, possibly leading to late adverse events and limiting late lumen enlargement or positive remodeling. Additionally, chronic inflammation and hypersensitivity reactions to stent polymers or metals can contribute to late complications [2]. Drug-coated balloons (DCB) deliver a uniform, broad antiproliferative drug without implanting a foreign body, thereby targeting the hyperplastic biology of restenosis. This approach ameliorates chronic inflammation, delayed endothelialization, and impaired vessel pulsatility, potentially reducing restenosis rates. The vessel can therefore undergo positive remodeling and maintain its natural biomechanical properties, potentially leading to late lumen enlargement and a reduction in neointimal hyperplasia, the primary cause of restenosis [3].

2.2 Pharmacologic Foundations of DCB Therapy

Structure DCB are typically semicompliant angioplasty balloons, similar in structure to standard angioplasty balloons. The key difference is that DCB have a surface coating composed of an antiproliferative drug integrated with one or more excipients. Efficient drug transfer during a brief inflation period depends on precisely controlling the coating's microstructure, surface energy, crystallinity, and interactions between excipient and drug. Preclinical studies using scanning electron microscopy and atomic force microscopy have demonstrated that microcracks, porosity, and coating heterogeneity substantially influence drug detachment dynamics during inflation [4]. These structural variables are also associated with coating microstructure, vessel wall contact, excipient selection, drug loss during transit, and tissue retention [3, 4].

A major historical limitation of polymer-free drug delivery is the absence of a controlled-release matrix. To overcome this, modern coating technologies employ excipients acting not only as drug carriers but also as transient hydrophilic "bridges," facilitating rapid dissolution

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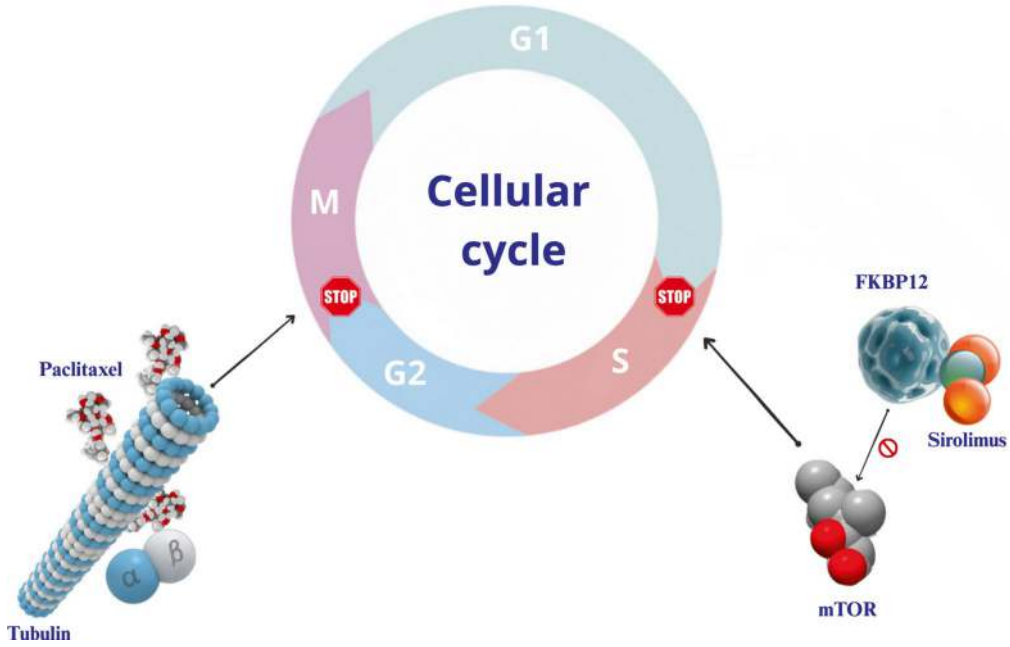


Fig. 2.1 Paclitaxel acts by penetrating arterial tissues and binding with high affinity to the β-tubulin subunit of the α/β-tubulin heterodimer, stabilizing microtubules and preventing their depolymerization. This irreversible stabilization disrupts cytoskeletal dynamics, leading to cell-cycle arrest at the G2/M phase and sustained inhibition of vascular smooth muscle cell proliferation and migration. Sirolimus and its analogues exert their cytostatic action through formation of a complex with FKBP12. This sirolimus–FKBP12 complex selectively inhibits the mTOR (mammalian target of rapamycin complex 1) pathway, producing reversible G1/S cell-cycle arrest in smooth muscle cells

and promoting efficient tissue binding. Animal models have shown that excipient–drug co-deposition, rather than drug alone, is essential for predictable penetration depth [5]. Thus, both the mechanical and chemical composition of the coating layer are critical determinants of therapeutic success.

Antiproliferative drugs (Fig. 2.1) The effectiveness of DCB-delivered agents relies on tissue uptake kinetics, penetration depth, cellular retention, and intracellular bioactivity. Lipophilic drugs, capable of crossing the hydrophobic core of endothelial cell membranes, are more readily transported to the arterial wall. The arterial wall acts as a reservoir for these hydrophobic drugs. Although the drug's mechanism of action is critical, its interaction with arterial tissue ultimately determines efficacy and toxicity [6]. Ex vivo perfusion studies reveal that lipophilic drugs tend to accumulate in arterial segments with higher lipid content, indicating that vessel composition influences local retention [7]. However, tissue interactions are often nonlinear and vary depending on microstructural features such as extracellular matrix density, lipid distribution, and inflammation.

Paclitaxel Paclitaxel (PTX) is a microtubule-stabilizing agent with strong antitumor effects. Its high lipophilicity and efficient uptake allow for prolonged retention in vessel walls, making it the main antiproliferative drug used in drug-coated balloons (Fig. 2.2). Evidence shows that paclitaxel can deeply penetrate arterial tissues and remain detectable for weeks after a brief exposure. In pig models, PTX levels in the arterial wall stay above the therapeutic threshold for up to 14–28 days, even with balloon contact times under a minute [8].

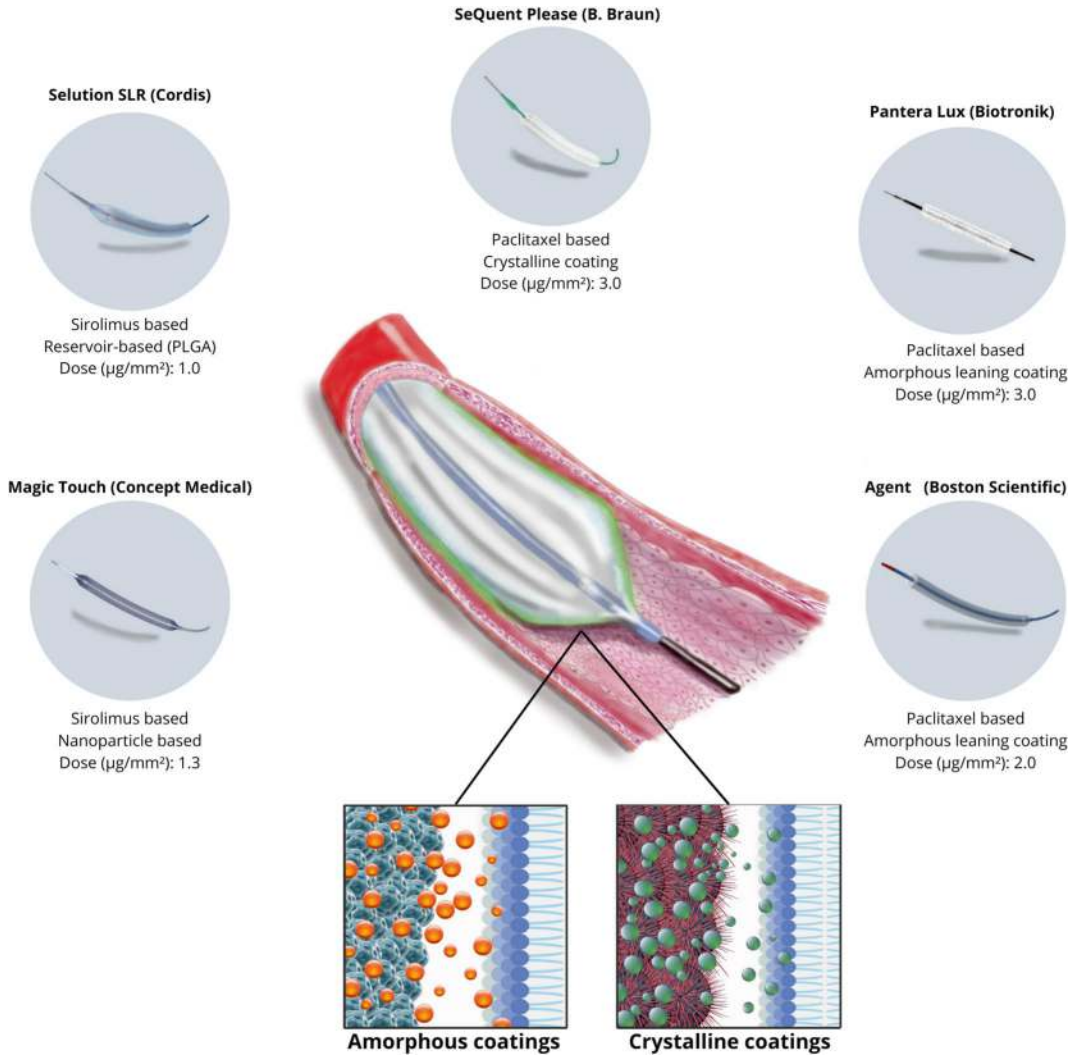


Fig. 2.2 Upper section: Drug-coated balloon and the different commercially available DCB platforms. Lower section: Coating strategies is drug-coated balloons rely on excipients that regulate drug adhesion during delivery and promote efficient transfer to the vessel wall. Coatings may be crystalline, offering greater stability and prolonged tissue retention but producing more particulate debris, or amorphous, which dissolve rapidly and provide faster release with lower stability

At equilibrium, PTX binds to tubulin in the tunica intima and adventitia, which have dense cytoskeletal networks. Its retention in deep arterial tissues helps sustain therapeutic drug levels. Inside vascular smooth muscle cells (VSMCs), paclitaxel irreversibly binds to the β-subunit of tubulin, stabilizing microtubules and inhibiting their disassembly. This disrupts normal cytoskeletal dynamics, halts cell cycle progression at the G2/M phase, and consequently reduces cell proliferation and migration—key mechanisms of hyperplasia [7, 8]. It has been shown that paclitaxel, at therapeutic levels, inhibits neointimal hyperplasia, thus playing a significant role in preventing restenosis [9]. Additional preclinical investigations suggest that PTX may also modulate inflammatory signaling, macrophage recruitment, and extracellular matrix turnover, all of which contribute to restenosis biology.

Sirolimus and analogs Sirolimus (rapamycin) is the most frequently used limus-based drug in drug-eluting stents (DES). It functions as a cytostatic agent by forming a complex with FKBP12 to inhibit mammalian target of rapamycin (mTOR), which leads to a reversible blockage of cell cycle progression from G1 to S phase in vascular smooth muscle cells. This action reduces smooth muscle cell proliferation without inducing the irreversible microtubule stabilization seen with paclitaxel. This process reduces proliferation and growth, key factors in neointimal hyperplasia and restenosis. While sirolimus is less lipophilic, its cleaner safety profile and potent anti-inflammatory properties have driven significant innovation in DCB technology.

Since sirolimus dissolves quickly and absorbs slowly, new-generation DCBs use specially designed excipients and nanostructured delivery systems to boost its lipophilicity and extend its stay in the arterial wall. Preclinical research with nanoparticle-encapsulated sirolimus showed notably better uptake rates and longer-lasting tissue levels compared to unbound sirolimus [6, 10].

Dose concepts Surface dose density must offset substantial drug loss during transit and the brief period for tissue absorption. Consequently, DCB have higher drug loads per surface area than DES. For example, PTX doses usually range from 2 to 3.5 μg/mm^2, while sirolimus doses range from 1 to 4 μg/mm^2, a pattern consistent across modern coronary and peripheral platforms [11]. Mathematical models indicate that acute loss during tracking can be over 60% for some crystalline coatings, requiring higher initial doses to guarantee effective deposition [12].

Importantly, higher dose density does not necessarily translate into higher tissue concentration, as excipient composition and microstructure modulate bioavailability more strongly than total drug mass. Preclinical models have shown that amorphous coatings with lower drug loads can outperform crystalline coatings with higher loads due to superior dissolution kinetics and better tissue penetration [12]. In fact, only 10–20% of the surface drug load is effectively deposited into the arterial wall [5].

Furthermore, a higher nominal dose on DCB does not lead to increased plasma levels. In fact, peak plasma PTX after a DCB inflation is 0.3–1.0 ng/ml immediately after the procedure and becomes undetectable within 24 h. Similarly, for sirolimus-based DCBs, peak concentrations are 0.5–2.0 ng/ml right after the procedure and also become undetectable within 24 h. In comparison, sirolimus DES maintain levels of 1–3 ng/ml for several days [13–15].

Coating materials Excipients in DCB coatings significantly affect pharmacokinetics by controlling drug retention on the balloon during delivery, enabling efficient and uniform transfer to vessel walls, and impacting particulate formation and tissue retention. Ideally, coatings should keep drugs on the balloon during navigation through the guidewire and vasculature. Once in place, they should promote consistent, effective drug transfer. Iopromide, a contrast agent, was the first excipient used. The drug coating's morphology can be crystalline or amorphous. A dedicated chapter of the book will go deeper into such details.

Crystalline coatings Often paired with PTX, are rigid and offer greater stability and drug retention, leading to more effective delivery and longer tissue retention. However, they are linked to increased downstream particulate generation, which could theoretically raise the risk of slow flow or periprocedural myocardial infarctions, though clinical evidence has not confirmed this [7, 8].

Amorphous coatings Dissolve readily, release drugs more quickly, but are less stable, leading to lower tissue retention and greater loss during transit. To enable sirolimus delivery, modern reservoir technologies for sirolimus include: submicron nanoparticles (Nanolutè), biodegradable micro-reservoirs with cell-adherent technology, poly-lactic-co-glycolic acid (PLGA) microspheres, and ion-pair complexes—designed to enhance sirolimus lipophilicity.

Mechanisms of drug transfer The transfer of drug from DCB coatings to the vessel wall involves a coordinated sequence of convection, desorption, diffusion, and tissue binding [4, 12]. Balloon inflation presses the drug–excipient film directly against the intima. The resulting pressure gradient drives rapid convection, initiating immediate intracellular and extracellular entry of the drug. As excipients dissolve, drug crystals or nanoparticles detach—a process described as pressure-induced desorption.

Factors associated with efficient drug transfer:

- Balloon pressure: Higher inflation pressures increase contact forces and compress the coating against the intimal surface, improving penetration depth. Excessive pressure, however, may increase particulate detachment.
- Inflation time: Approximately 70–80% of total drug transfer occurs within the first 30 s, with minimal incremental uptake after 60 s. This supports contemporary guidelines recommending 30–60 s inflations.
- Vessel wall composition: Calcification and fibrosis reduce permeability and disrupt drug distribution. Preclinical porcine studies show significantly lower drug deposition in segments with >30% calcium burden unless aggressive lesion preparation is performed.
- Balloon-to-artery ratio: An optimally matched diameter facilitates uniform drug–wall interface, minimizing shear-related coating loss while maximizing area of contact. It also decreases the risk of flow-limiting coronary dissection.

2.3 Specific Characteristics of Some Commercially Available DCB

2.3.1 Sirolimus Based

Selution SLR (Cordis, USA): Selution SLR is a sirolimus-eluting balloon featuring a surface dose of 1 μg/mm^2. Its main innovation lies in combining PLGA micro-reservoirs with a lipid-based Cell Adherent Technology (CAT™). This biodegradable polymer matrix anchors submicron sirolimus particles to both the balloon surface and the vascular wall upon deployment. The design aims to mimic the controlled, slow release typical of limus drug-eluting stents while maintaining a polymer-free lumen. In preclinical studies, this reservoir approach maintained arterial sirolimus levels for several weeks, providing even transmural distribution with minimal inflammation response [16].

Magic Touch (Concept Medical, USA): Magic Touch is a sirolimus-coated balloon (1.3 μg/mm^2) that uses the Nanolutè™ technology, in which sirolimus is encapsulated within phospholipid-based nano-carriers. These nanoparticles form an amphiphilic matrix that improves sirolimus solubility, shields the drug during transit, and facilitates rapid partitioning into the lipophilic arterial wall upon inflation [17]. In porcine coronary models, this platform produced high early tissue concentrations with sustained levels up to 28 days and significant reductions in neointimal area compared with uncoated balloons [18].

2.3.2 Paclitaxel Based

SeQuent Please (B.Braun, Germany): SeQuent Please is a paclitaxel-coated balloon (3 μg/mm^2) that uses iopromide as a hydrophilic contrast-based excipient. The iopromide–paclitaxel matrix creates a crystalline surface that holds the drug during delivery but enables effective transfer when inflated. Preclinical in vitro studies have demonstrated that this formulation achieves a drug transfer rate of approximately 17% of the loaded paclitaxel to the vessel wall, with the remainder either retained on the balloon or lost during delivery. This transfer rate is notably higher than other excipient formulations, such as ethanol/water or acetone-based coatings, which typically transfer less than 1% of the drug [19].

Pantera Lux (Biotronik, USA): Pantera Lux is another paclitaxel-coated balloon (3 μg/mm^2) that uses butyryl-tri-hexyl citrate as its lipophilic

plasticizer and carrier. This excipient helps the paclitaxel adhere firmly to the balloon surface and dissolve gradually into the vessel wall. The design aims to ensure good retention during navigation and controlled drug release at the lesion site. Electron microscopy and bench tests have revealed a smooth, uniform coating with limited particle shedding and predictable drug wash-off profiles, indicating a more "amorphous-leaning" microstructure compared to traditional iopromide-crystalline coatings [4, 20].

Agent (Boston Scientific, USA): Agent is a low-dose paclitaxel-coated balloon (2 μg/mm^2) that uses acetyl tri-n-butyl citrate as a lipophilic citrate ester excipient. This matrix aims to minimize particulate embolization and enhance controlled release, with a relatively smooth coating profile compared with earlier PCB generations. Preclinical evaluations in porcine models showed robust neointimal suppression without delayed healing [21].

2.4 Conclusion

The success of DCB depends on complex interactions between biophysical and pharmacological factors that control local drug delivery. These include coating stability during transit, drug transfer efficiency during inflation, and the ability for the tissue to retain the drug over time. Achieving this requires balancing drug characteristics such as lipophilicity, intracellular affinity, and mechanisms ranging from cytostatic to cytotoxic—with excipient chemistry and device-specific design features. Procedural factors like lesion preparation, balloon sizing relative to the artery, inflation pressure and duration, and the arterial wall's composition (e.g., fibrosis or calcification) also influence outcomes.

Different commercially available DCB platforms incorporate these principles through various technologies designed to overcome the limitations of short contact time for drug delivery. These devices differ not only in the antiproliferative drug used, such as paclitaxel or sirolimus, but also in dose density, crystal structure, and excipient complexity—from contrast-based hydrophilic matrices to biodegradable micro-reservoirs, phospholipid nanoparticles, and ion-pairing complexes. Consequently, these differences lead to variations in immediate drug transfer, arterial penetration depth, spatial distribution, and how long therapeutic levels are maintained. This reflects how advances in material science, vascular biology, and pharmacology combine to develop platforms that produce sustained antiproliferative effects without permanent implants.

Beyond mechanical and pharmacological factors, the clinical importance of DCBs lies in their ability to prevent restenosis effectively while avoiding problems associated with metallic stents, such as chronic inflammation, neoatherosclerosis, reduced vasomotor function, and the need for prolonged dual antiplatelet therapy. As sirolimus-based and hybrid coating technologies improve, early findings suggest they could expand indications, improve safety, and adapt better to different lesion types usually treated with DES. Ultimately, drug-coated balloons are an evolving approach to vascular restoration, offering a transient intervention that induces lasting biological changes while maintaining the vessel's natural structure, biomechanics, and functional integrity.

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3 Technical Insights on Drug-Coated Balloons, from Bench to Animal Studies: Paclitaxel

Marco Ferrone, Giuseppe Di Gioia, and Juan F. Granada

3.1 Introduction

Interventional cardiology has witnessed several revolutionary developments over the years leading to progressive and sometimes radical changes in daily practice. The most striking revolution in percutaneous atherosclerotic disease treatment has probably been the introduction of drug eluting stents (DES).

DES have shown outstanding outcomes in terms of efficacy and safety over the years, overcoming restenosis, the biggest limitation of the previous stent generation (i.e., bare metal stent BMS) [1, 2].

Despite the impressive performance, even the last generation of DES shows some flaws. Stent thrombosis (ST) is a rare unpredictable event resulting from delayed vessel healing, due to a hypersensitivity reaction to the drug, polymer coating, or their combination [3, 4] leading to catastrophic consequences. Moreover, in some specific settings, DES show lower efficacy probably due to the permanent metallic implant deployed in the coronary arteries potentially leading to sustained and prolonged inflammation, along with native vessel caging and loss of vasomotion (i.e., in-stent restenosis (ISR), long coronary stenosis, diffused coronary artery disease, and small vessels). Furthermore, the deployment of a scaffold requires a minimum period of double antiplatelet therapy (DAPT) causing apprehension in specific clinical settings, where a shorter DAPT period is desired (i.e., high bleeding risk patients).

The idea of creating a device allowing a local drug delivery but avoiding the downsides of a permanent implant was already pursued with the creation of the bioresorbable scaffold (BRS).

Unfortunately, despite the initial promising results of BRS, an alarming increase in scaffold thrombosis (ST) in patients treated with BRS leads to the discontinuation of this device's application for the treatment of coronary atherosclerosis.

Drug-coated balloons (DCB) represent an alternative to BRS when a "leave nothing behind" approach is desirable. At this regard, the discontinuation of BRS program in 2017 in the coronary setting boosted the development of DCB in the last decade.

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Table 3.1 Technical and biological DCB features

Technical and biological DCB features			
Drug	Immediate transfer into the vessel wall	Prolonged retention into the vessel wall (Lipophilic properties)	No systemic toxic effect
Coating	Homogeneous coating thickness and drug concentration along the balloon surface	Quick drug release	Coating fragmentation into submicron particles to allow drug delivery after balloon inflation
Balloon catheter	Minimal drug loss during tracking	Minimal drug loss on inflation	Optimal vessel wall contact on inflation

Truthfully, the concept of delivering antiproliferative drugs via balloon angioplasty has been around for several decades. The first "proof-of-concept" experiment dates back to 1986 when Goldman et al. demonstrated effective delivery of horseradish peroxidase to dogs and human arteries using a multiple lumen polyurethane catheter [5]. Since then, several models and drugs have been tested to find out the best combination of drug and delivery system. As a matter of fact, the concept of a balloon-based drug delivery looks straightforward at first, but several biological and technological issues should be considered to develop an effective DCB technology (Table 3.1).

3.2 Technical Features

The concept of developing a balloon-based drug delivery system to prevent arterial restenosis was founded on the hypothesis that a durable effect on neointimal proliferation could be achieved following a single-drug delivery [6]. Drug delivery is a key point for a successful and durable angioplasty. Last generation DES release –Limus family drugs, revealed to be the most effecting class of drug preventing restenosis when eluted from an implanted scaffold for several weeks through a controlled and prolonged release profile. DCB drug release, on the contrary, is way different from DES-based concept technology and its success relies on a rapid transfer of a single dose of antiproliferative agent expected to be retained as much as possible into the vessel wall for an extended antiproliferative effect.

Heparin was one of the first drugs tested for a local delivery by Edelman et al. in 1990, but those experiments showed that the drug was not retained for a proper period of time into the vessel wall once released [7]. In 1992, Muller et al. experimented Methotrexate [8] and in 1995 Colchicine was tested as well [9]. All these studies, showing a rapid washout of the delivered compounds, weakened the enthusiasm toward this technology. The first agent showing promising results in this setting was identified in 2001 by Professor Bruno Scheller who found out that Paclitaxel solubility was significantly increased when mixed with contrast agents and its repeated intracoronary bolus injection combined with iopromide resulted in significant reduction of neointimal proliferation in the porcine model of restenosis [10]. The idea of combining antiproliferative drug with contrast medium was then applied to a balloon to create the first validated DCB at experimental level [11]. These early clinical results boosted again the interest in this field and several DCB programs started, trying to reproduce and to improve this approach using different carriers as a method to transport paclitaxel into the vessel wall after a balloon dilatation.

Due to its lipophilic profile, to its potent antiproliferative effect, and to its chemical stability following tissue delivery, the first generation of DCB commercially available was all loaded with Paclitaxel.

Paclitaxel has shown to inhibit cell proliferation and migration due to an irreversible stabilization of intracellular microtubules, resulting in the inhibition of cell replication during the meta-

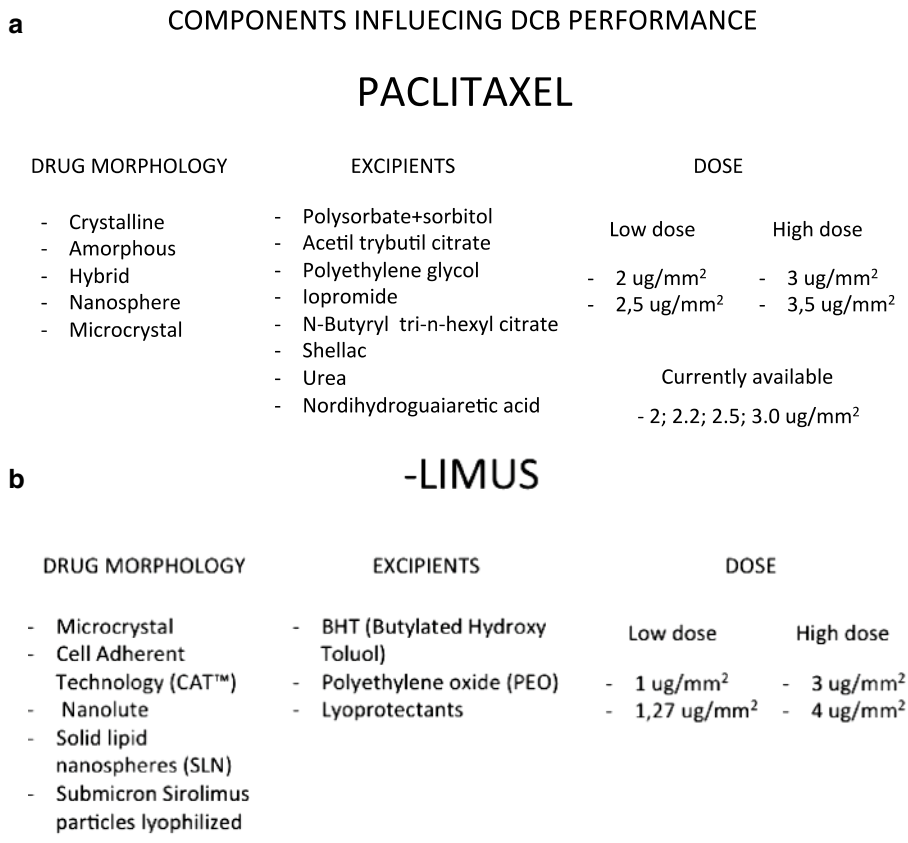


Fig. 3.1 (**a**) Paclitaxel-eluting balloon components. (**b**) –Limus-eluting balloon components

phase and the anaphase of mitosis [12]. Although being loaded with the same drug, DCB differ on several aspects because of different manufacturing processes (i.e., drug morphology, excipients, drug dose) (Fig. 3.1a).

In 2018, a meta-analysis showing increased mortality in patients treated with paclitaxel eluting balloon raised concerns about this devices safety and companies started to look for an alternative drug. Following the DES experience, the natural choice for an alternative drug was Sirolimus. Sirolimus and its analogs (–limus drugs) reversibly binds to FKBP 12 and potently inhibits cell proliferation by forming a complex with the mammalian target of rapamycin, thus blocking cell cycle progression at the juncture of the G1 and S phases. Despite Sirolimus was the natural choice and the natural evolution of drug coated balloon, this drug chemical characteristics are unsuitable for the DCB approach as many differences distinguish Sirolimus and Paclitaxel in their kinetics, effect, and safety behavior (Fig. 3.2). For this reason, many efforts were made to develop an ideally effective Sirolimus-eluting balloon technology able to release an effective drug dose below the toxic boundary trying to resemble a sustained and stable concentration into the vessel wall over time (Fig. 3.3). Many formulations and different Sirolimus isoforms were tested to obtain such an effect (Fig 3.1b).

Attribute	Sirolimus(or Analogs)	Paclitaxel
Mode of Action	Cytostatic	Cytotoxic
Margin of safety	10000-fold	100-fold
Therapeutic Range	Wide	Narrow
Anti-Restenotic	Yes (Higher)	Yes
Anti-Inflammatory	Yes	No
Tissue Absorption	Slow	Fast
Tissue Retention	Short	Long

Fig. 3.2 Paclitaxel and Sirolimus characteristics (drug dose effect without excipients)

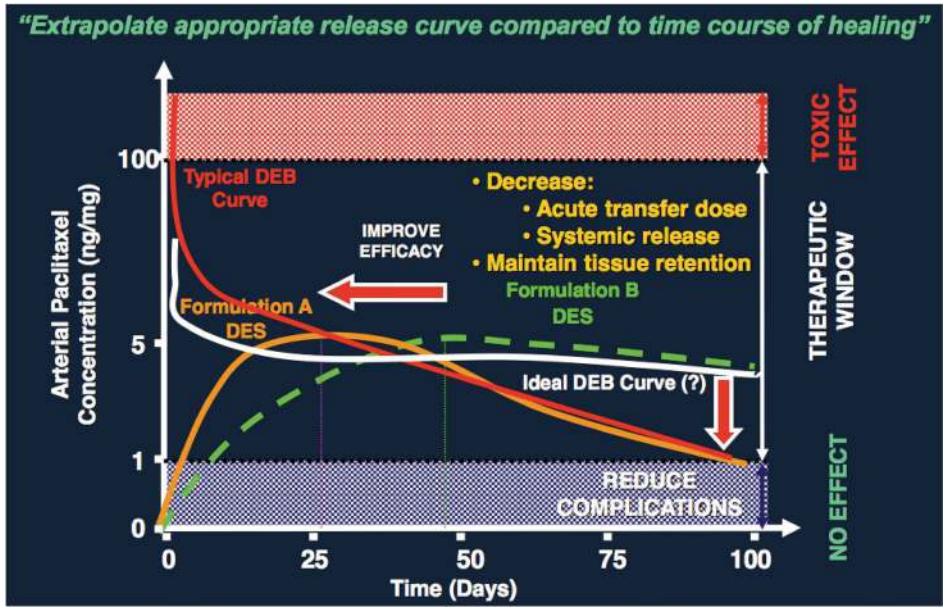


Fig. 3.3 Ideal DCB kinetics curve. The single-drug dose released during DCB inflation should be above the minimal effective dose but below the upper limit of toxicity. The drug concentration into the vessel wall should remain stable overtime resembling the DES behavior. DCB drug coated balloon, DES drug eluting stent. (Modified by B. Cortese (2014))

3.3 Morphology

3.3.1 Paclitaxel

Paclitaxel can be processed in many morphologies (crystalline, amorphous, hybrid, nanosphere, microcrystals), although the most common morphologies applied to DCB are crystalline and amorphous. Studies have demonstrated how the morphology can influence the pharmacokinetic profile of the drug, its deposition, and its bioavailability [13]. Crystalline Paclitaxel, in particular, allows a prolonged retention of the drug into the vessel wall at the cost of a significant downstream particle loss during balloon inflation and tracking, that can reach 20–25% of the total dose, as demonstrated from Kelsch et al. for a urea- or iopromide-based DCB in an in vivo model [14], or even 42%, as showed from Berg et al. for a iopromide-based formulation during in vitro passage through a hemostatic valve and a guiding catheter [15]. Amorphous morphology, on the contrary, can be easily processed to reproduce a more uniform coating onto the balloon surface although having a shorter retention after deployment. More interestingly, as shown in a preclinical animal model comparing crystalline to amorphous coating, Paclitaxel morphology doesn't affect the acute drug deliver [13]. In this report, the drug concentration in the arterial tissue results comparable soon after the angioplasty in both groups. Significant differences rise starting at 1 h after the balloon inflation when the crystalline-treated group maintains stable drug tissue levels, while the segments treated with the amorphous coating show a dramatic drop off (99%) in the Paclitaxel concentration. At 1 week, both formulations display a significant vessel washout (crystalline 88.6%, amorphous 99.9%) even if the drug remains detectable until 28 days in both groups (tissue half-life for paclitaxel delivered by the crystalline and the amorphous was 7.5 and 3.4 days, respectively). Furthermore, a comparative analysis of the vessel surface Paclitaxel concentration in respect of arterial wall concentration showed a much higher presence of the drug on the surface at 24 h, 7 and 28 days in the crystalline group. Conversely, in the amorphous group, the vessel surface and the arterial wall concentrations were similar at 1 and 24 h. After 24 h, the vessel surface concentration declined further in comparison with the arterial wall levels [13]. The most interesting consideration about Paclitaxel delivery with DCB is that the massive amount of drug eluted onto the vessel surface (~20 orders of magnitude higher compared with the drug eluted from a paclitaxel eluting stent over time) doesn't show toxic consequences at any time. Probably, the finding that after 7 days arterial tissue concentrations begins to equalize the vessel surface levels, which is the explanation of the lack of tissue toxic effects seen in experimental studies, despite the apparent supratherapeutic tissue levels found immediately after PCB use. Plus, at 30 days, the arterial tissue levels of paclitaxel seen in the crystalline group were comparable to the levels seen in the paclitaxel eluting stent control group, maintaining a concentration within the therapeutic range for inhibition of smooth muscle proliferation but below cytotoxic limit [13].

3.3.2 Sirolimus

Sirolimus kinetics is not ideal for the drug delivery and retention into the vessel wall. Thus, many efforts were made in order to find an efficient formulation with better kinetics profile. Crystalline, amorphous, and mixed formulation were tested showing better drug delivery and retention with the crystalline morphology compared to mixed and amorphous formulation [16]. Other formulations applied to SEB were encapsulation of submicron sized Sirolimus drug into highly biocompatible drug carrier phospholipid; creation of biodegradable polymer containing micro-reservoirs released by amphipathic lipids and lipids nanospheres releasing Sirolimus into the vessel wall; local liquid drug delivery obtained by means of an inflation of a drilled balloon spilling a liquid solution of submicron Sirolimus particles lyophilized with lyoprotectants throughout the balloon to artery contact (Table 3.2). Several studies are investigating the effect of SEB in specific setting.

Table 3.2 Commercially available coronary SEB

Device	Drug	Technology/Excipient	Dose (ug/mm^2)	Company	Approval
Selution	Sirolimus	Cell Adherent Technology (CAT™) Amphipathic Lipid Carrier	1	Med Alliance	CE certified IDE for small vessels and ISR ongoing
SeQuent Please SCB	Sirolimus	Butylated Hydroxy Toluol (BHT)	4	BBraun	CE certified
Magic Touch	Sirolimus	Nanolute technology (Phospholipid-Based Excipient)	1.27	Concept	CE certified IDE for ISR ongoing
Mozec SEB	Sirolimus	Solid lipid nanospheres (SLN) consisting of Sirolimus + lipid	3	Meril	CE certified
Biolimus A9 BCB	Biolimus A9	Polyethylene oxide (PEO)	3	Biosensors International	–
Virtue	Liquid sirolimus	Submicron Sirolimus particles lyophilized with lyoprotectants	N.A.	Orchestra Biomed	–

SEB sirolimus eluting balloon, *CE* Conformité Européenne, *ISR* in-stent-restenosis, *IDE* investigational device exemption

3.4 Excipients

Paclitaxel lipophilicity prevents its early washout from the target site, nevertheless, this intrinsic property hiders its transfer from the balloon to the vessel surface. Cremers et al. clearly demonstrated this concept comparing a balloon catheter coated with Paclitaxel in a water-soluble matrix to a balloon coated with plain Paclitaxel [17]. Plain Paclitaxel cannot be delivered efficaciously into the vessel and needs to be linked to substances increasing its solubility in the water. Excipients play an essential role in this setting and largely impact on the balloon outcome as they can deeply change Paclitaxel tissue pharmacokinetic [17, 18]. For this reason, many efforts have been made to develop the best formulation and the available DCB are loaded with several different coating made up of different excipients (Fig. 3.1a). It is really hard to define which formulation is the more suitable to this technology; some excipients are mixed up with the drug only with pharmacokinetic purposes (e.g., X-ray contrast medium, urea, PEG etc.), while others with additional treatment purposes (e.g., resveratrol as antioxidant). That said, finding the best excipient and the best manufacturing process to create the coating (pressure, temperature, and drying time to fix the coating onto the balloon) is not straightforward, and it deals with the research of a perfect balance between coating adhesion on the balloon surface and a good release at the moment of the contact with the vessel wall. Kempin et al. tested, at this purpose, five different coating: four obtained from mixing up Paclitaxel with different excipients (ethanol, ethanol + PVP, ethyl acetate, acetone) and SeQuent Please (B. Braun, Melsugen AG, Germany) DCB coating. This study shows how each coating conveys completely different behavior to the balloons resulting in different drug morphology, different percentage of drug loss and drug transferred to an in vitro model possibly affecting outcome in a clinical setting (Fig. 3.4) [19].

Unlike Paclitaxel, Sirolimus biggest limitation regards its lack of penetrating properties due its hydrophilic nature. For this reason, SEB excipients aim to increase Sirolimus lipophilicity. For this reason, each SEB has a unique excipient working along with the Sirolimus encapsulation to favor the penetration and the retention of the drug inside the vessel wall. Polyethylene oxide

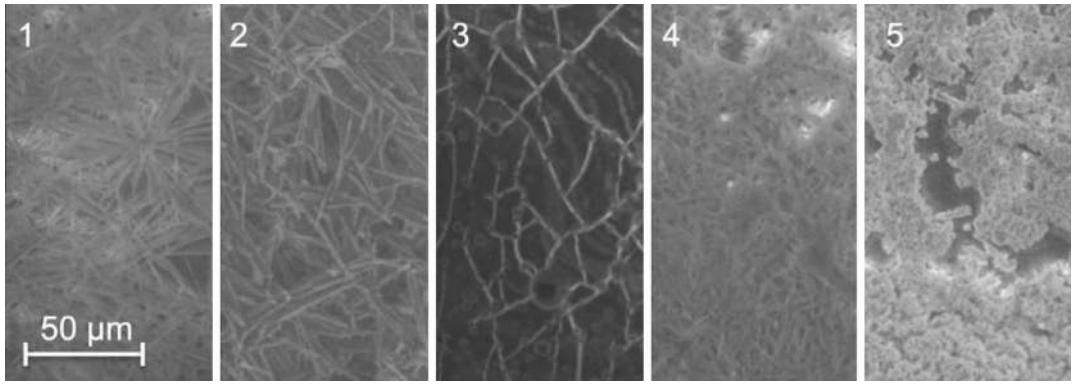


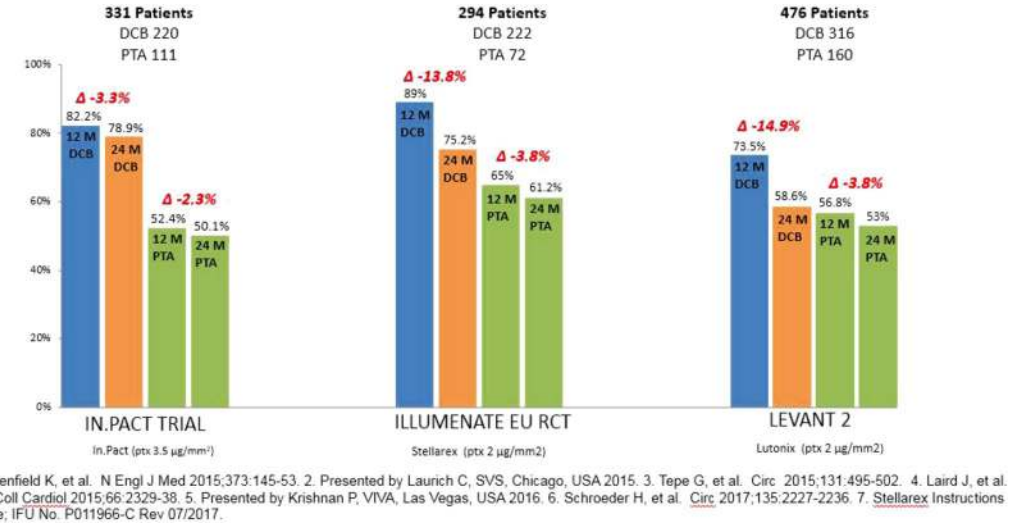
Fig. 3.4 Paclitaxel morphologies resulting from different coating technique, electronic microscope images: (1) ethanol, (2) polyvinylpyrrolidone + ethanol, (3) ethyl acetate, (4) acetone and (5) SeQuent Please balloon [21]

(PEO) and Butylated Hydroxy Toluol (BHT) are some of the excipients used in the currently manufactured SEB. Every technology is created to maximize the drug performance in terms of penetration and retention over time. Data regarding the different behaviors of different formulation are available in the literature. The combination of high dose of Sirolimus (4.00 ug/mm^2) crystalline form and butylated hydroxytoluene (BHT) as an additive shows a prolonged retention of Sirolimus in the vessel wall with 40–50% of drug found in the vessel wall after 1 month [16]. Biolimus A9 used to develop a novel SEB shows tenfold higher lipophilic properties than Sirolimus, maintaining the same mechanism of action. Pre-clinical test on coronary porcine model demonstrates an effective performance of Biolimus after 28 days from the procedure [20].

3.4.1 Drug Dose

The last important consideration about DCB technical features is the drug dose. Paclitaxel can effect cells replication based on dose and exposition time as demonstrated from in vitro experiments [21]. As no direct comparison has been made among the available balloon in commerce, it is really hard to define which dose is the optimal one to achieve the best long-term patency. The literature about this topic is currently misleading showing high dose balloon superiority in some cases [22, 23] or substantial equity between low dose and high dose balloons in other experimental models [24]. Currently, drug dose of PEB commercially available is shown in Fig. 3.1. Randomized clinical trials only compare each DCB to PTA and show different percentage of primary patency at 1 and 2 years (Fig. 3.5). Even if this Figure shows results which clearly seem to endorse one balloon among the others, this data cannot be compared each other's, and specific trials are demanded to obtain validated assessment.

Resembling the PEB scenario, companies developed different SEB with different drug concentration. Higher dose (4 and 3 ug/mm^2) and lower dose (1 and 1.27 ug/mm^2) SEB are available in the market. Due to lower lipophilicity, Sirolimus effect highly depends on the manufacturing process, on the carrier and on the excipients making the variability of its effect depending on many factors beyond the concentration applied on the balloon. Direct comparisons are strictly necessary to fully demonstrate the efficacy of each device compared to the others.



1. Rosenfield K, et al. N Engl J Med 2015;373:145-53. 2. Presented by Laurich C, SVS, Chicago, USA 2015. 3. Tepe G, et al. Circ 2015;131:495-502. 4. Laird J, et al. J Am Coll Cardiol 2015;66:2329-38. 5. Presented by Krishnan P, VIVA, Las Vegas, USA 2016. 6. Schroeder H, et al. Circ 2017;135:2227-2236. 7. Stellarex Instructions for Use; IFU No. P011966-C Rev 07/2017.

Fig. 3.5 12 and 24 months primary patency of In.Pact, Medtronic Peripheral, Playmouth, USA (high dose DCB), Stellarex, Spectranetics, Colorado Spring, USA and Lutonix, Bard Peripheral, Tempe, USA (Low dose DCB)

3.5 Safety

The great enthusiasm arisen from DCB introduction was hampered from the theoretical concerned about safety. First of all, as previously mentioned, one of the most common consequence and, at the same time, one of the most important goal of a DCB is to release as less particulate as possible during its tracking and during its inflation. Unfortunately drug loss is an actual issue as demonstrated by several experimental bench and in vivo tests [14, 25, 26]. The percentage of drug lost into the bloodstream varies according to balloon studied [25, 26] and, more importantly, the quantity of particulate loss downstream largely depends on the PTX type of coating. Crystalline PTX is much prone to distal embolization than amorphous formulation [24, 25]. Particulate loss is associated with degeneration in non-target distal vascular bed, consisting of fibrinoid changes in small arterioles with or without adjacent skeletal muscle necrosis. In spite of these evidences, the real implication of the embolization in humans is not still defined and we could find only one case-report in literature involving a 72-year-old woman who underwent elective SFA angioplasty of a previous bare metal stent experiencing an allergic event after treatment with a DCB. One week after the index procedure, the patient presented with a prominent, mildly painful rash on the distal aspect of her left lower limb (ipsilateral to the DCB) extending from lower thigh to ankle. Histologic examination of biopsy tissue showed prominent fibrin deposition consistent with fibrinoid necrosis of the arterioles and mononuclear infiltrate, as well as thrombosis of surrounding small vessels together with diffuse infiltrates of neutrophils and eosinophils, resembling the findings of preclinical safety evaluation [27]. Vessel healing is the second big safety concern raised against DCB. One of the big problems of the first generation DES eluting PTX was the high drug concentration released at the target site resulting in local toxicity with the development of aneurysm and thrombosis [28, 29]. The drug released at one time from the DCB is much more concentrated than the drug released from the DES but interestingly the PTX distribution over the whole vessel area exposed to the balloon contact is much more regular with a less degree of inflammation when compared to a Paclitaxel eluting stent [30] as confirmed from the safety outcome rate coming from the clinical trial (Fig. 3.6).

	LEVANT II[1]		Global[2]	IN.PACT SFA[3]	Global Clinical Cohort[4]		EU RCT[5]		US Pivotal[6]		Global[7]
	PTA	Lutonix 035		PTA	IN.PACT Admiral		PTA	Stellarex	PTA	Stellarex	Stellarex
Subjects	160	316	691	111	220	1406	72	222	100	200	371
All Thrombosis				3.7% (4/107)	1.4% (3/207)	2.9% (38/1311)			0.0% (0/95)	1.1% (2/189)	
Revasc. due to Thrombosis	0.7% (1/140)	0.4% (1/285)	1.3% (8/634)								
Major Amputation	0.0% (0/140)	0.3% (1/286)	0.5% (3/635)	0.0% (0/107)	0.0% (0/207)	0.2% (3/1311)	0.0% (0/60)	0.0% (0/204)	0.0% (0/95)	0.0% (0/189)	[7]

1. Rosenfield K, et al. N Engl J Med 2015;373:145-53.
2. Presented by Laurich C, SVS, Chicago, USA 2015.
3. Tepe G, et al. Circ 2015;131:495-502.
4. Presented by Jaff MR, VIVA, Las Vegas, USA 2016..
5. Presented by Brodmann M, AMP, Chicago, USA 2016.
6. Stellarex Instructions for Use; IFU No. P011966-C Rev 07/2017.
7. Presented by Zeller T, LINC, Leipzig, Germany 2017. One major amputation reported, but total number of subjects evaluated at 12 months for this endpoint is unavailable.

Fig. 3.6 12 months key safety outcomes from randomized clinical trials

Nevertheless, the meta-analysis published in 2018 raising the hypothesis of higher mortality in patients treated with Paclitaxel-eluting balloon (subsequently rejected by other clinical evidences) provided an important boost to SEB development. As per PEB, Sirolimus embolization and potential release during the balloon tracking and balloon dilatation highly depend on the drug formulation and processing. Crystalline/microcrystalline isoforms are the more prone to embolization but in this setting no concerns about safety have ever been raised due to the drug broad safety profile [31–36].

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4 Technical Insights on Drug-Coated Balloons from Bench to Animal Studies: -Limus Drugs

Stefano Garzon, José Mariani Jr., Guy F. Prado, and Pedro A. Lemos

4.1 Introduction

Drug-coated balloons (DCB) are interventional tools intended to provide local delivery of bioactive agents to the vessel wall, with clinical applications that are still growing in spectrum [1–22]. They are complexly built devices, with an intricate interplay involving the drug, carrier, excipient, and the balloon itself that ultimately have an impact on the final therapeutic result [23]. Currently available DCB vary substantially among each other in their constituents, and, as of today, a class effect does not seem probable. It is, therefore, central to examine the technical details of present DCBs to better understand their individual characteristics. In this chapter, we aim to describe the technicalities of DCB using agents of the -limus family, which became available only recently as a drug for DCB.

4.2 Pharmacology

Sirolimus is a cytostatic drug, initially approved by the Food and Drug Administration (FDA) for renal transplant patients in 1999 [24]. It is a potent inhibitor of cell proliferation, binding reversibly to the FKBP 12 subunit of the transforming growth factor beta 1 (TGF-β1) receptor and forming a complex with the mammalian target of rapamycin (mTOR), blocking the cell cycle at G1 phase and inhibiting smooth-muscle cell proliferation both in vitro and in vivo [25–27]. As with other macrolides, it also presents anti-inflammatory action by hampering pro-inflammatory cytokine-dependent response [28, 29]. Sirolimus was first tested as an anti-restenotic drug in coronary stents in the early 2000s [30]. Eventually it would outperform paclitaxel and drugs from the -limus family would become the dominant and later the only anti-restenotic drug for coronary stents [31].

Compared to paclitaxel, sirolimus has wider safety and therapeutic margins, as well as a more intense anti-inflammatory effect. However, it is less lipophilic, takes longer to be absorbed by the vessel wall, its tissular retention is shorter, and it may need constant tissular levels for longer periods in order to be effective [32]. A comparison between the pharmacological characteristics of sirolimus and paclitaxel is presented in Table 4.1.

Table 4.1 Comparison of pharmacological features of paclitaxel and sirolimus

Characteristic	Paclitaxel	Sirolimus
Lipophilicity	Higher	Lower
Therapeutic margin	Narrower	Wider
Safety margin	Narrower	Wider
Anti-inflammatory effect	Lower	Higher
Cellular effect	Cytotoxic	Cytostatic
Safety margin	Narrower	Wider
Drug uptake	Faster	Slower
Local drug retention	Longer	Shorter

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4.3 Drug Loss

Due to the way DCB are manufactured, usually with the drug being sprayed onto an angioplasty balloon, drug retention on the balloon surface is more fragile than in DES, and drug shedding along the route of the device until reaching its intended target in the vessel segment is an expected phenomenon.

Experimental studies have demonstrated varying degrees of drug loss during the manipulation of DCB in vitro and in vivo, and these fluctuate greatly depending on the drug formulation used in each DCB. Hydrophilic and crystalline formulations present higher rates of drug loss as opposed to hydrophobic and amorphous formulations. However, the former are more easily transferred into the vessel wall. Sirolimus balloons using the hydrophobic excipient butyryl-trihexyl citrate (BTHC) had significantly less drug loss during manipulation when compared with a urea-based balloon (8.1% vs. 35.5%). Drug uptake was higher in the urea-based preparation (30.1% vs. 16.9% for urea- and. BTHC-based balloons, respectively), but complete saturation of the binding sites (both specific and non-specific) was achieved with both preparations, suggesting that the two formulations might have comparable efficacy [33]. Another study, investigating different coating formulations and doses of a sirolimus-coated balloon, demonstrated surprisingly low levels of drug loss with a crystalline formulation during balloon manipulation through guiding catheter, hemostatic valve, and blood (2 ± 14%) [34], illustrating how variable drug loss can be with different DCB (Table 4.2).

4.4 Drug Uptake

As with paclitaxel-coated balloons, sirolimus needs a carrier to deliver the drug to the vessel wall. Different combinations of phospholipids, polymers, and carriers containing the encapsulated drug are used in different DCB [35–37]. This transfer needs to be rapid and effective, as the drug must be delivered within 30–60 s of balloon-to-wall contact. Sirolimus diffusion from the luminal surface into the deeper layers of the vessel occurs gradually over days. In an animal model, 1 h after balloon deployment, most of the sirolimus was confined to the luminal surface, with no drug beyond the internal elastic lamina. Most of the drug would only reach the media 7 days after balloon deployment [36].

The lower lipophylia of sirolimus vs. paclitaxel may play a role in tissue uptake and retention. Additionally, data suggest that drug uptake can be severely hampered or even completely prevented by an intact intima [38]. Thus, dissections are instrumental in facilitating drug diffusion through atherosclerotic plaques [39]. Plaque characteristics also seem to influence drug retention, with atheroma potentially serving as a drug reservoir by hampering drug washout [40]. Calcified and lipidic plaques appear to be less permeable to drug diffusion, with higher rates of drug retention in the intimal layer of soft plaques (i.e., plaques without calcium or lipid deposits) when compared with hard plaques (i.e., plaques with calcium and/or lipid deposits) [33]. Particle size also seems to influence drug uptake, with a potential advantage for nano-sized drug carriers [41].

Table 4.2 DCB eluting sirolimus available in the 2025 market

Device	SeQuent SCB	Magic Touch	Selution
Drug	Sirolimus	Sirolimus	Sirolimus
Concentration	4 μg/mm^2	1.27 μg/mm^2	1 μg/mm^2
			3 μg/mm^2
Excipient	Sirolimus-butylhydroxytoluol (BHT)-matrix	Phospholipids (nanocarrier)	Biodegradable polymer (micro-reservoirs), CAT (cell adherence technology)

4.5 Systemic and Local Drug Concentrations

For a DCB to be effective, local retention of the drug and its diffusion from the intima into the deeper layers of the arterial wall must be maximal. On the other hand, as it is a local treatment, systemic levels must be minimal. Various animal studies have investigated systemic and tissular concentrations of sirolimus following DCB angioplasty. In one study, systemic sirolimus levels were higher in the first 30 min following balloon-inflation (9.3 ng/mL), and then decreased rapidly in the first 24 h (0.8 ng/mL). When compared with a sirolimus-based stent, systemic levels at 30 min and 24 h were consistently lower than those found following stent deployment (13.3 ng/mL and 4.6 ng/mL, respectively). Local concentration of sirolimus was higher immediately following balloon-inflation, but after 2 weeks, sirolimus was still detectable in the vessel wall (140.6 ng/mL and 15.5 ng/mL, respectively). Conversely, these tissular levels were consistently higher than those found in the sirolimus-based stent (4.5 ng/mL and 1.6 ng/mL, respectively) [36].

In another study, different crystalline formulations of a sirolimus-coated balloon were found in consistently higher concentrations in the vessel than with amorphous formulations at 1-month evaluation, with approximately 50% of the initial dose of sirolimus still present at the deployment site. Also, systemic concentrations of sirolimus at 10 min were well-within the accepted safety margins (3.79 ± 0.87 ng/mL and <5–10 ng/mL, respectively) [34].

4.6 Distal Embolization

Downstream drug shedding from drug-coated balloons is a recognized phenomenon, particularly with crystalline paclitaxel formulations. Torii and colleagues, using a porcine model, found signs of distal embolization in skeletal muscle with three different paclitaxel-coated balloons ranging from 25% to 42.9% [42]. In another study, two different paclitaxel-based drug-coated balloons used to treat peripheral artery disease were tested for distal embolization in downstream tissues. At 90 days, urea-based formulations had significantly higher skeletal muscle concentrations of paclitaxel than those found in polysorbate/sorbitol formulations (0.6 ng/g and 16.1 ng/g, p 0.009, respectively) [43]. Combined formulations of sirolimus and paclitaxel, as tested by Kawai and cols, showed that downstream embolization was lower in the combined drug balloon, with 0% of segments with tissue injury in the subjects treated with the combined balloon vs. 23% of segments in the subjects treated with the paclitaxel balloon (p 0.018). In the combined drug group, 18% of segments showed signs of distal embolization vs. 50% in the paclitaxel group (p 0.026) [44]. Aihara and colleagues compared distal embolization of three different drug-coated balloons (two paclitaxel-based and one sirolimus-based) in rabbits. Surprisingly, the sirolimus-coated balloon presented higher muscle/artery ratio concentrations when compared with the paclitaxel-coated balloons, indicating a higher risk of distal embolization with the sirolimus balloon. Distal skeletal muscle drug concentrations were very low for paclitaxel balloons, and significantly lower when compared with the sirolimus balloon (0.25 ng/mg vs. 0.66 ng/mg vs. 28.07 ng/mg for both paclitaxel ballons and the sirolimus balloon, respectively, with $p < 0.001$ for the comparisons of both paclitaxel balloons vs. the sirolimus balloon) [45]. This data is somewhat conflicting with most of the experimental evidence, where downstream embolization is a common event, particularly with paclitaxel-coated balloons with crystalline formulations, and less common with sirolimus DCB. Some potential drawbacks of this study and future directions have been depicted later [46, 47].

In clinical practice, manifestations of distal embolization such as slow-flow phenomenon and reduction of coronary flow reserve have been observed with DCB. In below-the-knee angioplasty, the use of paclitaxel DCB has been associated with slow-flow, which hinders wound healing and increases the chances of lower-limb

amputations. Slow-flow occurred in 18.6% of patients undergoing angioplasty with DCB. The incidence of wound healing at 730 days was 77% vs. 91% (p 0.03) and the incidence of amputation was 40% vs. 14% in those with and without no-reflow, respectively. Slow-flow was independently associated with limb amputation (HR 3.9 [1.6–8.9], $p < 0.01$) and worse wound healing (HR 0.5 [0.3–0.9], p 0.02) [48]. When compared with paclitaxel-coated balloons, sirolimus-coated balloons appear to have a reduced incidence of slow-flow [49]. Young and cols. investigated the impact of angioplasty using a paclitaxel-coated balloon in coronary flow reserve (CFR), measuring basal, post-balloon angioplasty (POBA) and post-DCB angioplasty CFR values. Basal and post-POBA values were similar, but CFR values decreased significantly following the use of DCB (1.59 ± 0.49 vs. 1.22 ± 0.28, $p < 0.0001$) and gradually increased over time, with distal embolization and microvascular impairment being a possible explanation to these findings [50–53].

4.7 Conclusions

Sirolimus-coated balloons are a promising technology. Sirolimus is the anti-restenotic drug of choice for DES, due to its favorable pharmacological characteristics and proven safety. Like all DCB, each individual sirolimus-coated balloon has different characteristics, and the operators must take these into account when deciding which DCB to use in their patients. As with paclitaxel-coated balloons, clinical evidence regarding the efficacy of sirolimus-coated balloons is gradually emerging for ISR and de novo coronary lesions. The next chapters of this book will shed light on the novel DCB applications.

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The Role of Crystalline Coating for DCB

5

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Abbreviations

DCB	Drug-coated balloon
DES	Drug-eluting stent
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
PCB	Paclitaxel-coated balloon
PES	Paclitaxel-eluting stent

5.1 Why DCB?

During the early development phase of drug-mediated percutaneous coronary interventions (PCI), it was assumed that a prolonged and sustained drug release from a drug eluting stent (DES) over weeks to months is mandatory for an effective inhibition of restenosis. As clinical research continued, Scheller et al., however, showed that only a short time of exposition between a drug releasing device, e.g., from a balloon surface, and vessel wall was required to promote an effective inhibition of neointimal proliferation [1].

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5.2 What Is the Reason for this?

The principle of a drug-coated balloon (DCB) is to deliver a sufficient amount of an antiproliferative drug to the lesion and to assure that it persists within the lesion long enough to prevent restenosis after mechanical widening. To achieve such a prolonged (similar to DES) drug effect, after only a short drug transfer, two prerequisites need to be met. On one hand, the antiproliferative drug needs to show a low dissolution behavior in blood during delivery to prevent premature drug loss. On the other hand, the drug needs to be released and transferred into the lesion at the target site immediately during balloon inflation. Similarly, the drug needs to have a high persistence within the vessel wall for at least 4 weeks. The reason for this requirement concerning drug persistence is based on observations made in animal models. Within this 4-week period, most of neointimal proliferation was observed so that valuable information to quantify neointimal hyperplasia can be obtained. Prolonged periods may only provide information about safety but are less appropriate as efficacy endpoints. Thus, Schwartz et al. [2] reported that due to vascular healing processes following mechanical widening of the artery, the 28-day time point is appropriate to evaluate device efficacy.

Consequently, a 28-day time point is suitable for both PD and PK studies in animals, whereas the desired drug concentration within the target artery after DCB treatment should be in the range

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which is commonly reported following DES implantations.

Paclitaxel is the best investigated drug for DCB-mediated treatment of coronary and peripheral artery disease. The combination of paclitaxel with the contrast agent iopromide (SeQuent Please Neo) has the largest body of evidence resulting in more than 110 publications demonstrating its safety and efficacy in preventing restenosis. For the mechanism of action, both its antiproliferative character and its physicochemical properties are proposed to be of importance. Due to its highly lipophilic character, paclitaxel has a very poor solubility in aqueous solutions of only 0.3 µg/ml (molarity 0.35 µM) at 37 °C, making it an ideal agent to be used as the active pharmaceutical ingredient of a drug-coated balloon [3].

5.3 Crystalline vs. Amorphous Modification

The dissolution rates of a drug coated on a balloon can be modified by its crystal modification. For many drugs, and for paclitaxel in particular, different polymorphisms exist such as amorphous, crystalline anhydrate, crystalline monohydrated, and crystalline di-hydrated [4]. In contrast to crystal structures, the amorphous form does not describe a state of the highest order. The atomic or molecular arrangements of amorphous structures are more irregular. The different crystal modifications with the varying molecular distances and the resulting binding forces cause different physico-chemical properties such as melting points, melting ranges, or solubilities. Since more energy is required to break down the crystal lattices than to overcome the binding forces of amorphous structures, the solubilities of crystalline modifications are below those of the amorphous form. It is assumed that the efficacy of a paclitaxel-coated balloon is caused by its long persistence in the vessel wall. A single application of paclitaxel by means of a DCB leads to effective artery concentrations over at least 4 weeks [5].

Considering that crystalline structures are thermodynamically more stable than their amorphous counterparts, a longer persistence in crystalline formulations would be expected. This was stated by Granada et al. [6] who compared drug retention of crystalline and amorphous paclitaxel formulations within the vessel wall after 4 weeks. Taking this into consideration, crystalline drug formulations are beneficial and therefore preferred for DCB. Furthermore, DCB are not permanent implants and consequently late stent associated complications are avoided while having comparable drug retention within the artery wall in the case of a crystalline paclitaxel coating.

According to the findings of Granada et al. [6] who studied paclitaxel concentrations in porcine coronary arteries, concentration of amorphous paclitaxel decreased by 99% within only 24 h, whereas the artery concentration of crystalline paclitaxel formulation remained at the same level. After 28 days, only 0.04% of the amorphous paclitaxel was measured in the vessel. For the crystalline formulation, 9.2% of the baseline paclitaxel concentration was measured at 28 days (Fig. 5.1).

Looking at pharmacodynamic endpoints that have also been addressed by Granada and coworkers, a relation between both PK and PD is apparent. Neointimal inhibition and fibrin deposits are both stronger in the crystalline formulation group as compared to the group with the amorphous formulation, which supports paclitaxel's persistent influence in terms of safety and efficacy [6]. The former parameters need to be evaluated at later time points. In the porcine coronary model, between 3 and 6 months after treatment, neointimal proliferation and inflammation were normalized so that no significant differences between DCB and POBA were detected (Fig. 5.2) [7].

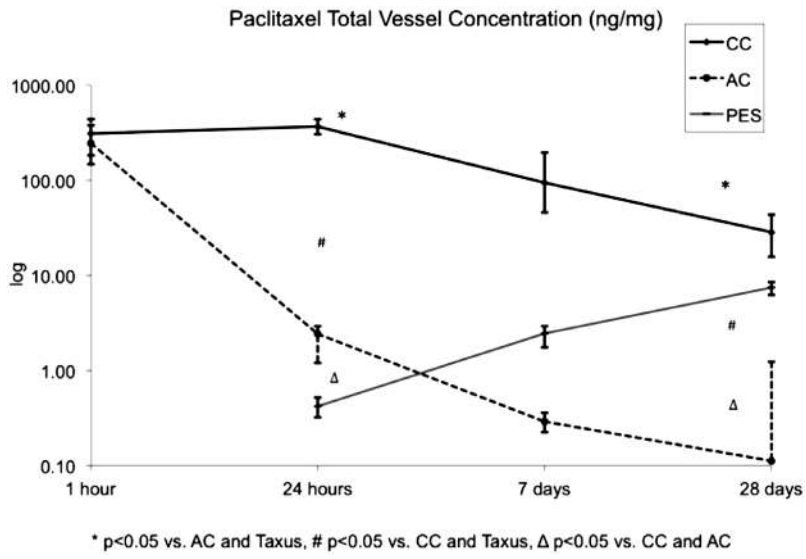


Fig. 5.1 Graphic representation of the 28-day paclitaxel tissue levels of both paclitaxel-coated balloon Coatings in comparison with the Taxus stent (PES). *AC* amorphous, *CC* crystalline, *PES* paclitaxel-elutingstent. (Granada et al. [6], Copyright 2014)

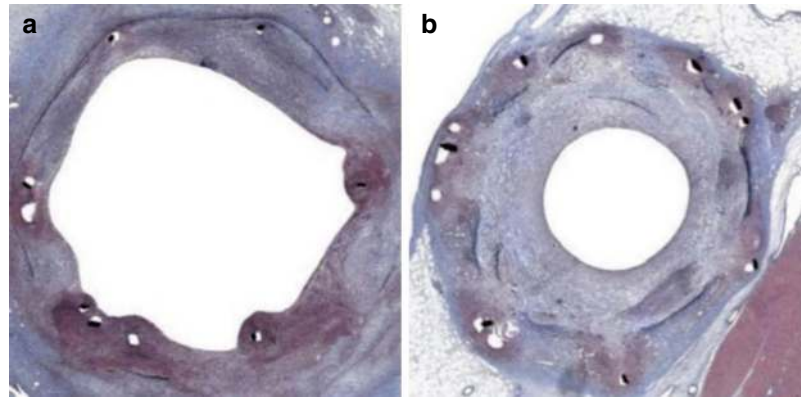


Fig. 5.2 Representative histological pictures of CC (**a**) and AC (**b**) at 28 days in porcine coronary arteries following paclitaxel-coated balloon delivery. (Granada et al. [6], Copyright 2014)

Besides paclitaxel, there is another commonly used drug to treat coronary and peripheral artery disease: sirolimus (or rapamycin). So far mainly paclitaxel is used for DCB angioplasty, whereas sirolimus and its analogs are the drug of choice for DES. What is the reason for this and what are the differences between paclitaxel and sirolimus?

Paclitaxel and sirolimus address different signal transduction pathways and they differ in their physico-chemical properties. The cellular target of paclitaxel is the microtubule structure. Paclitaxel binds irreversibly on this target, so that the disassembly of the microtubules will be permanently inhibited [8]. Consequently, proliferation and migration of cells are stopped. Microtubule structures are ubiquitous, e.g., they occur in the cell core, within the cell organelles and even outside of cells to promote cellular movement. In short, they occur in numerous parts of a cell, giving paclitaxel a great potential to bind and to persist. In contrast, sirolimus exerts its pharmacological effect only via a reversible, non-permanent, enzyme interaction. Sirolimus interacts with the immunophilin FKBP12 and the resulting FKBP12-sirolimus complex binds to the FRB domain in mTOR and therefore allosterically inhibits the mTORC1 kinase activity [9].

Considering this pharmacodynamical mode of action, sirolimus has less potential for artery persistence than paclitaxel. Furthermore, the physico-chemical properties especially the solubility in aqueous solutions should be compared between paclitaxel and sirolimus.

Both are highly lipophilic compounds and therefore show poor solubility in water, making them appropriate for a DES or DCB application. However, paclitaxel is even more lipophilic than sirolimus and therefore has a lower solubility in water (0.3 μg/ml vs. 2.6 μg/ml) [3, 10].

Considering these differences between paclitaxel and sirolimus within their target binding sites and their physico-chemical properties, it is even more crucial and challenging for a sirolimus-coated balloon to achieve a sufficiently long drug persistence in the vessel wall to reach the desired therapeutical effect.

The allosteric inhibition of the drug target cannot be influenced to achieve better drug persistence. However, from a thermodynamical point of view, the solubility and thereby the drug persistence in the vessel wall might be modified by choosing a crystalline instead of an amorphous drug formulation (alternatively to the release from polymers on stents).

To investigate this, Clever et al. [11] compared different DCB coating formulations containing amorphous sirolimus, mixture of amorphous and crystalline sirolimus and crystalline sirolimus regarding sirolimus persistence in the artery wall and neointimal inhibition after 28 days in swine, respectively. Like paclitaxel-coated balloons, crystalline formulations of sirolimus coated on

Table 5.1 Selection of preferred coating: sirolimus content of 3.5 × 20 mm on sirolimus-coated balloon catheters before and after use in porcine coronary arteries, drug content of treated vessel segments 10 min post balloon inflation and 1 month later

Coating	AS 1	AS 7	IIIb	Vb 4	Vb 7
Premounted stent	Yes	No	Yes	No	Yes
Sirolimus on unused balloons = dose (μg/mm^2)	0.9	7	7.1	3.8	6.8
Loss in valve, guiding catheter, and blood, in vitro study (% of dose, $n = 4$)	No data	No data	No data	2 ± 14	No data
Sirolimus in arterial wall, 10–30 min post balloon inflation, $n = 6$					
(μg [total amount])	17 ± 4	16 ± 12	96 ± 64	139 ± 44	224 ± 52
(ng/mg tissue)	57 ± 13	53 ± 40	219 ± 118	488 ± 287	547 ± 139
(% of dose)	8.6	0.85 ± 0.64	5.1 ± 3.4	14.4 ± 4.6	12.5 ± 2.9
Sirolimus in arterial wall, 1 month post treatment, $n = 6$ (ng/mg tissue)	0.8 ± 0.7	1.0 ± 1.0	2.2 ± 1.8	129 ± 101	136 ± 112
(% of dose)	0.12	0.03 ± 0.03	0.1 ± 0.0	7.5 ± 6.9	4.7 ± 3.8
Decrease of sirolimus content in vessel wall over 1 m (% of initial amount in the vessel wall, based on mean values)	99	97	98	48	62
Residual sirolimus on used balloons (% of dose, $n = 6$)	26 ± 7	No data	9.2 ± 1.6	6.3 ± 1.5	2.7 ± 0.8

AS amorphous sirolimus coating, *IIIb* less amorphous sirolimus coating, *Vb* crystalline sirolimus coating
Clever et al. [11]. Copyright 2016

balloons could demonstrate higher drug persistence after 28 days. The decrease of sirolimus content in the vessel wall after 28 days was 97–99% for the amorphous and partial amorphous formulation, whereas up to 50% of the initial transferred sirolimus amount of the crystalline formulation persisted over 28 days. Looking at the absolute sirolimus concentration in the artery wall, the amorphous and the partial amorphous formulation reached 1–2 ng/mg, whereas the crystalline formulation obtained an artery concentration of 129 ng/mg (Table 5.1).

Angiographic and histomorphometrical analysis (e.g., max. neointimal thickness or diameter stenosis) did reveal antirestenotic activity in all sirolimus-treated vessel segments without any statistical significance between amorphous and crystalline coating formulations, but in favor of the crystalline sirolimus-coated balloon [11] (Table 5.2; Fig. 5.3).

The underlying reason for this finding might be that the animal model is not as sensitive for sirolimus as it is for paclitaxel. This is confirmed by the previous preclinical studies, which compared sirolimus eluting stents and bare-metal stents mounted on paclitaxel-coated balloons. Based on these porcine studies, the inhibition of neointimal proliferation was higher for the paclitaxel releasing devices compared to their sirolimus counterparts [12, 13].

Regarding safety parameters, histological findings such as vasculitis, myocarditis, or focal inflammation were mostly mild or moderate. Histopathological findings were not limited to the treatment groups but also occurred with the uncoated balloons. Even in the high dose group, with more than 15 μg/mm^2 crystalline sirolimus in one vessel segment, no vessel occlusion was observed. Furthermore, left ventricular angiography was performed to assess possible downstream effects of amorphous and crystalline particles on myocardial function. There were no differences in left ventricular ejection fraction between amorphous and crystalline sirolimus particles [11]. Therefore, regarding downstream particles there is no safety concern due to lower solubility of crystalline sirolimus particles.

In lieu of the above-mentioned findings, there is evidence to assume that crystalline drug formulations for SCBs may be the preferred coating technology.

Table 5.2 Summary of quantitative coronary angiography and histomorphometry in-stent at 1 month follow-up

Var	Uncoated control, *n*	Value uncoated control	AS 1, *n*	Value AS 1	Vb 4, *n*	Value Vb 4	Vb 7, *n*	Value Vb 7	SQP, *n*	Value SQP	*P* value
RFD initial, mm	12	2.61 (2.42–2.74)	13	2.69 (2.50–2.86)	13	2.78 (2.66–2.82)	12	2.75 (2.54–2.92)	13	2.60 (2.55–2.79)	0.4875
MLD post, mm	12	3.13 (2.95–3.34)	13	3.17 (2.94–3.36)	13	3.26 (3.17–3.35)	12	3.27 (2.95–3.38)	13	3.17 (2.95–3.32)	0.8712
Overstretch (−)	12	1.20 (1.16–1.24)	13	1.13 (1.08–1.29)	13	1.16 (1.09–1.22)	12	1.17 (1.15–1.25)	13	1.17 (1.13–1.21)	0.8817
MLD FU stent, mm	12	1.90 (1.62–2.58)	12	2.39 (1.92–2.60)	12	2.63 (2.22–2.75)	12	2.62 (2.31–2.87)	12	2.96 (2.66–3.10)	0.0020
LLL in-stent, mm	12	1.01 (0.61–1.36)	12	0.71 (0.39–1.13)	12	0.66 (0.47–0.81)	12	0.62 (0.44–0.82)	12	0.22 (0.12–0.38)	0.0002
Diastenosis in-stent, %	12	26.5 (6.83–34.1)	12	3.70 (−3.16–26.2)	12	1.31 (−7.51–16.0)	12	5.45 (−8.45–9.87)	12	−8.45 (−13.5—0.68)	0.0043
Vessel diameter, mm	12	3.15 (2.85–3.39)	8	3.13 (3.07–3.29)	11	3.25 (3.06–3.40)	11	3.22 (3.04–3.34)	11	3.32 (3.26–3.47)	0.5800
Lumen diameter, mm	12	2.61 (2.25–2.88)	8	2.69 (2.63–3.04)	11	2.91 (2.72–3.04)	11	2.74 (2.50–3.05)	11	3.02 (3.00–3.23)	0.0532
Max neonint thick, mm	12	0.65 (0.46–0.78)	8	0.43 (0.34–0.56)	11	0.36 (0.28–0.44)	11	0.38 (0.30–0.66)	11	0.29 (0.25–0.30)	<0.0001
Vessel area, mm^2	12	7.87 (6.50–9.06)	8	7.99 (7.22–8.44)	11	8.27 (7.39–9.28)	11	8.33 (7.41–8.59)	11	8.83 (7.14–9.49)	0.6827
Lumen area, mm^2	12	3.20 (2.72–5.09)	8	4.33 (3.63–5.90)	11	4.94 (4.53–5.74)	11	5.65 (3.23–5.96)	11	6.16 (4.94–7.38)	0.0096
Neointimal area, mm^2	12	4.08 (3.00–4.84)	8	3.10 (2.47–3.64)	11	2.78 (2.68–3.46)	11	2.90 (2.57–4.25)	11	2.39 (2.08–2.84)	0.0196
Injury score (−)	11	3.0 (2.9–3.0)	7	2.9 (2.2–3.0)	4	3.0 (2.6–3.0)	8	3.0 (3.0–3.0)	5	3.0 (3.0–3.0)	0.1749
Inflammation score (−)	11	2.8 (2.6–3.0)	7	2.5 (2.0–3.0)	4	2.9 (2.5–3.0)	8	3.0 (2.9–3.0)	5	3.0 (3.0–3.0)	0.2424
Diameter stenosis, %	12	17.8 (12.3–20.3)	8	12.0 (7.72–14.1)	11	11.0 (8.00–12.4)	11	10.6 (8.63–17.4)	11	7.66 (6.73–9.01)	0.0026
Area stenosis, %	12	58.5 (41.0–63.6)	8	43.0 (29.6–48.7)	11	36.0 (30.3–44.0)	11	34.2 (30.8–52.8)	11	26.6 (24.7–32.0)	0.0005

At the time of treatment: vessel reference diameter (RFD initial; mm), minimal lumen diameter in-stent after implantation (MLD post), and vessel overstretch after stent implantation (overstretch). At 1 month angiography: minimal lumen diameter in-stent (MLD FU stent), late lumen loss in-stent (LLL in-stent), and diameter stenosis in-stent (diasten in-stent), negative values mean persistent overstretch. Histomorphometry: vessel diameter, lumen diameter, maximum neointimal thickness, vessel area, luminal area, neointimal area, injury score, inflammation score, diameter stenosis, and area stenosis. Values are medians with interquartile range; *P* value is based on the *F* test in a mixed model with repeated measures based on ranks.
AS amorphous sirolimus coating, *SQP* paclitaxel-coated SeQuent Please balloon; *Vb* crystalline sirolimus coating
Clever et al. [11]. Copyright 2016



Fig. 5.3 Representative histological examples. Top left, Uncoated control; top right, AS. Bottom, from left to right: Vb 4, Vb7, SeQuent Please. AS indicates amorphous sirolimus coating; and Vb, crystalline sirolimus coating. (Clever et al. [11]. Copyright 2016)

5.4 Particle Release During DCB Angioplasty

5.4.1 What Is the Impact of Coating Particles After DCB Angioplasty?

On one hand, coating particles are part of the DCB's mode of action. Particles are released by balloon inflation and transferred into the artery wall where they persist due to crystalline deposits ensuring a DES-like drug effect. Over time, the drug (e.g., paclitaxel or sirolimus) will be dissolved from these crystalline deposits, subsequently fulfilling their therapeutic effects. Dissolved paclitaxel and sirolimus molecules bind to their specific cellular targets, thereby mediating arterial transportation and distribution. Thus, Levin et al. [14] reported that due to its specific binding to FKBP12 sirolimus distributes evenly through the vessel wall. In contrast, paclitaxel, which binds to the microtubules, remains in the subintimal space and further penetrates into the adventitia (Fig. 5.4).

On the other hand, the release of particles in arteries is viewed critically and is a frequent point of discussion in expert committees. From the technical perspective, particle release might cause distal embolization, which might be followed by the slow flow phenomenon. However, to evaluate the impact of DCB coating particles on distal embolization, one needs to keep in mind what happens during routine angioplasty. Diseased arteries that need to be opened mechanically by means of a balloon and/or stent catheter, usually contain endogenous plaque material. This debris will unavoidably be released during angioplasty and carried distally. Most of this plaque material consists of lipids and extracellular matrix components which are insoluble in water/blood. This in turn makes such particles significantly more relevant and critical compared to drug coating particles in terms of their duration

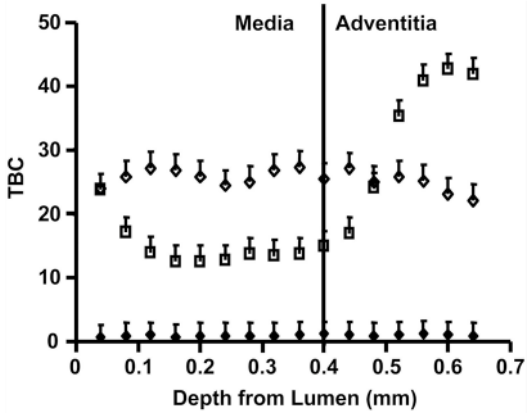


Fig. 5.4 Transmural equilibrium distribution of labeled dextran (♦), paclitaxel (□), and rapamycin (◇) in 0.040-mm-thick bovine internal carotid tissue segments. (Levin et al. [14], Copyright (2004) National Academy of Sciences, USA)

in the particulate state. However, the total amount that will be released and the particle size is important for distal embolization. To assess, the plaque burden that is released during balloon angioplasty and stent implantation, it is worthwhile to look at the investigations of Rogers et al. [15] who collected particulate debris after saphenous vein graft stenting with filters. The total embolic load per lesion collected in filters was in the range of 2–83 mm^3, with a mean volume of 23 ± 19 mm^3. This volume of particulate debris arising from endogenous plaque material exceeds the maximum of coating particles released during DCB treatment by far. Thus, the highest overall drug load of a coronary DCB is around 2 mg for the largest size, corresponding to a volume of approximately 2 mm^3, which is only one tenth of the mean volume reported by Rogers et al. Besides, it needs to be emphasized, that not all of the DCB coating will be embolized. Depending on the drug formulation, some drug will already be washed-off during introduction within the hemostatic valve and guiding catheter. The drug is also transferred into the arterial wall for therapeutic effects, whereas some drug will remain on the balloon, further reducing the possible overall embolic burden [16].

Moreover, Angelini et al. [17] investigated the size of endogenous plaque material released during coronary stenting. Particle sizes up to 2500 µm have been reported, whereby for 35% of the patients, particles larger than 1000 µm were detected. In contrast, most particles released during DCB treatment are significantly smaller than 50 µm.

From a technical point of view comparing size and volume of released particles, DCB are unlikely to increase embolic risk. Having investigated the embolic risk after DCB treatment in 343 patients with coronary DES-ISR (ISAR-DESIRE 3 trial) Colleran et al. [18] confirmed this assumption. The patients were treated either with POBA, with DES or DCB. As a marker of myocardial necrosis due to distal embolization, troponin changes were compared between the three groups. The results show very low troponin levels for all treatment groups with no significant differences between the groups, demonstrating no higher risk of embolization for DCB.

Finally, another indication for DCB angioplasty would be the neurovascular field. Vajda et al. [19] studied the use of DCB in neurovascular in-stent restenoses. 51 patients underwent 63 balloon interventions with either POBA (32%) or SeQuent Please DCB (68%). In most of the interventions (93.6%), no complications occurred and patients tolerated the procedure well. Neurological deficits due to embolization immediately after treatment were not reported.

Nevertheless, there were two major complications involving one fatal intracranial and a non-fatal subarachnoid hemorrhage, both without evidence for embolism.

Regarding the efficacy aspect 8 months after the intervention, the rate of recurrent stenosis (degree of stenosis ≥50%) for the POBA group was 50% and only 9% for the SeQuent Please DCB group [19].

Since DCB are successfully used in intracranial vessels without failures in postinterventional neurological activity, embolic risk due to DCB coating particle release, in particular crystalline particles, does not seem to be a clinical issue.

Above all the clinical benefits of the crystalline formulations clearly outweigh the risks of complications such as embolism.

5.5 The Clinical Perspective

Two decades ago, the interventional community was engulfed in competing clinical programs with the objective to study the safety and efficacy of first-generation DES. The Cypher and Taxus DES were in the race to demonstrate better efficacy for sirolimus or paclitaxel to combat neointimal hyperplasia and restenosis. Head-to-head comparisons of these DES revealed more favorable results for the Cypher stent [20]. But there was more than meets the eye. It was not just a battle of drugs, it was a competition of the polymer/drug matrix from which sirolimus, or paclitaxel were eluted into the coronary lesions. Likewise, there is the same complexity in the field of DCB. The mere presence of the drug on the balloon surface is only half of the story. The drug/excipient matrix, the balloon surface, and its coating morphology (or crystalline modification) are of paramount importance. About 15 years ago, the term ice/snow was coined to describe the physical appearance of the coating. Much attention was paid to the relationship between the bioavailability to the target cells and to the coating morphology. A purely ice-like appearance was not associated with better efficacy. The real magic happens, when only little of the drug/excipient matrix gets lost in transit to the lesion, and when it is sufficiently bioavailable at the target site with a minimal amount of drug/excipient particles washed away distally.

Clinical evidence created with paclitaxel-coated balloons (PCB) is currently larger as compared to their sirolimus-coated counterparts. As with the "Cypher vs. Taxus" evidence base [20], the coating formulation is the key to efficacy as stated in the ESC Guidelines on myocardial revascularization [21] which pointed out that there is no 'class effect' for PCB to treat ISR. This leaves the uncomfortable notion whether pooling of studies with different DCBs, even pooling paclitaxel or sirolimus DCB subgroups, will provide further evidence despite the statistical power of meta-analyses.

To grossly simplify coating technologies independent of the active drug component, there are amorphous and crystalline coatings depending on the excipients, the balloon surface characteristics, and the coating technology. In 2008, the first PCB was introduced to the market with a balloon coating that appeared to be more amorphous (Eurocor's DIOR). While amorphously coated PCB delivered favorable clinical results in uncontrolled trials for ISR [22] and de novo lesions [23], a direct comparison to the crystalline Paccocath coating (paclitaxel/iopromide, B. Braun's SeQuent Please) revealed a higher TLR rate for the DIOR DCB [24] suggesting that the amorphous paclitaxel matrix coating was less effective to reduce neointimal hyperplasia. Besides the amorphous modification, the lack of an excipient as a matrix builder has been discussed as the reason for the treatment failure of the first generation of DIOR DCB. Consequently, differences in efficacy to treat ISR do exist as recognized by the above-mentioned ESC guidelines. Further evidence that the crystallinity of the coating is an important element for efficacy can be derived from a comparative study investigating two crystalline coating technologies. Schroeder et al. investigated paclitaxel/iopromide and paclitaxel/butyryl-tri-hexyl citrate balloon coatings to treat ISR [25]. They could not find any difference between the two technologies in terms of TLR (11.8% vs. 9.6%, $P = 0.622$). However, it needs to be emphasized that the coating matrix is essential for DCB efficacy and sufficiently powered randomized trials need to confirm their benefit in clinical practice. Another crystalline coating technology (TransPax, Agent DCB, Boston Scientific) was compared to the paclitaxel/iopromide Paccocath technology by Hamm and coworkers [26]. Their study had the primary angiographic endpoint of late lumen loss (LLL) with the objective to show non-inferiority to the Paccocath PCB. Their findings revealed a non-inferior LLL for the TransPax coating as compared to the Paccocath PCB. This may have been favored by the smaller than expected LLL standard deviation of only 0.3 mm in their sample size calculation while less than expected analyzable angiographic data were available.

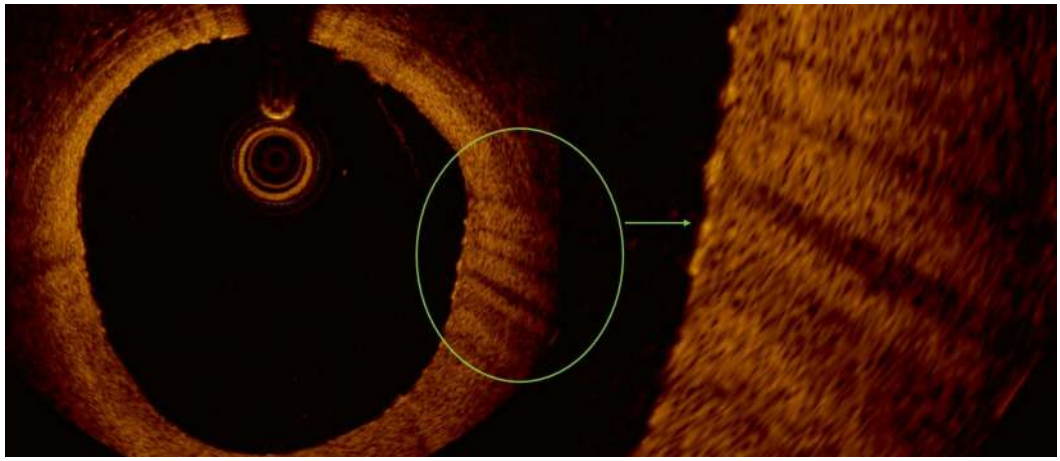


Fig. 5.5 Intracoronary artery visualization of crystalline sirolimus deposits after drug-coated balloon angioplasty (courtesy of Dr. Victor Jiménez, Vigo, Spain)

While clinical evidence from studies investigating DCB with crystalline paclitaxel coating suggests better efficacy, the use of sirolimus in various coating morphologies may show a different picture. Currently, there are three sirolimus coating balloons available. Clever et al. [11] studied various formulations resulting in amorphous and crystalline coatings. They concluded that there was a more effective acute drug transfer followed by a more effective drug persistence over 28 days for the crystalline as compared to a more amorphous coating in the porcine model. This formulation, i.e., a sirolimus dose of 4 μg/mm^2 balloon surface using a butylated hydroxyl toluene (BHT, SeQuent SCB, B.Braun) as an excipient was used in ISR [27, 28] and de novo [29] randomized controlled trials. The SCORE all-comers observational study [30] revealed an acceptably low target lesion failure rate of 3.5% in all-comers patients with de novo lesions (Otto et al. Late Breaking Trial, EuroPCR 2026, ClinicalTrials.gov Identifier: NCT04470934).

Jiménez and Íñiguez [31] visualized intracoronary crystalline deposits of sirolimus/BHT particles and their endothelial distribution through intracoronary imaging. In their case report, optical coherence tomography (OCT) imaging at the index procedure revealed hyper-echoic particles in the endothelium. The intensity of the echoes was similar to those created by stent struts. At 28 days, most of these hyper-echoic particles were no longer visible on the endothelial surface suggesting that their drug content was already released into the lesion site. The remaining particles that still remained within the intima, were available for an ongoing drug release process from these very small drug reservoirs thereby enabling longer drug effects (see Fig. 5.5).

Different sirolimus-coated balloon formulations which utilize micro-reservoir technology with a sirolimus concentration of 1 μm/mm^2 or nano-encapsulation with a sirolimus concentration of 1.4 μm/mm^2 have also been studied. In the SELUTION De Novo trial, which compared a sirolimus-eluting balloon (SEB) based strategy to a provisional DES strategy revealed that the SEB-strategy was non-inferior to contemporary DES in terms of target vessel failure (5.3% vs. 4.4%, p = 0.02) [32]. The results of the TRANSFORM II trial will provide additional evidence whether nano-encapsulation is equally effective awaited [33].

In conclusion, the existing clinical evidence indicates that a crystalline coating morphology, regardless of the drug, is both- effective and safe for the treatment of ISR and de novo lesions [34–36].

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6 Clinical Differences Between Crystalline and Amorphous DCB

Filippo Luca Gurgoglione, Irfan Ullah, and Bernardo Cortese

6.1 Principles and Mechanisms of Drug-Coated Balloon (DCB) Technology: Does a Class Effect Exist?

Drug-coated balloon (DCB) technology is designed to deliver an antiproliferative drug directly to the coronary vessel wall without the need for a permanent metallic scaffold or polymeric carrier [1].

The key principle of DCB angioplasty lies in the combination of mechanical vessel dilation and localized pharmacological action. During balloon inflation, typically lasting between 30 and 60 s, the drug is rapidly released and absorbed into the target vessel wall. This short but efficient exposure achieves a high local concentration of the antiproliferative agent at the site of injury, thereby inhibiting vascular smooth muscle cells (VSMCs) proliferation and reducing restenosis, while preserving the vessel's native anatomy and vasomotor function [2, 3].

A DCB system comprises three essential components:

1. a semi-compliant angioplasty balloon,
2. an antiproliferative drug, and
3. a drug carrier and excipient that retains the drug on the balloon during delivery and facilitates its transfer to the arterial wall upon inflation [4].

An effective DCB coating must ensure stable drug adhesion during catheter advancement, efficient transfer to the endothelium during inflation, and minimal loss into the bloodstream. Drug lipophilicity and excipient chemistry are key determinants of sustained therapeutic concentrations within the vessel wall during the critical period of neointimal proliferation (first 2–4 weeks after angioplasty) [5].

Therefore, the efficacy and safety of a DCB are determined by the complex interplay among drug type and dose, coating formulation (crystalline or amorphous), excipient composition, and coating technique. As a result, no "class effect" exists among DCB, and each platform reflects the unique properties of its specific design.

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6.2 Paclitaxel-Coated Balloons

For over a decade, paclitaxel-coated balloons (PCB) have represented the only DCB technology available for clinical use [6, 7].

6.2.1 Mechanism of Action

Paclitaxel is a highly lipophilic compound that allows rapid diffusion through cell membranes. Once internalized by VSMCs, paclitaxel binds to the β-subunit of tubulin, promoting microtubule polymerization and preventing their natural disassembly. This stabilizing effect arrests cell division at the G_2/M phase, leading to a potent and sustained antiproliferative response that inhibits neointimal hyperplasia [8, 9].

Experimental evidence demonstrates that local paclitaxel delivery significantly reduces neointimal area, intima-to-media ratio, and percent diameter stenosis compared with plain balloon angioplasty (POBA). These antiproliferative effects are most pronounced between days 3 and 21 after treatment, corresponding to the peak phase of neointimal growth inhibition [10, 11].

6.2.2 Coating

Paclitaxel can exist in either crystalline or amorphous form, each associated with distinct pharmacokinetic and biological properties [12]. The choice of excipient and coating process plays a crucial role in determining drug stability, tissue uptake, and long-term vascular retention, thereby influencing both pharmacodynamic characteristics and clinical performance [13].

6.2.2.1 Crystalline PCB in Clinical Practice

First-generation PCB featured a dehydrated crystalline paclitaxel layer designed for gradual dissolution and sustained drug release within the arterial wall, maintaining therapeutic tissue concentrations for up to 30 days. The crystalline structure favors the formation of intraluminal drug depots within the vessel wall, ensuring prolonged antiproliferative activity and effective suppression of neointimal hyperplasia.

However, crystalline coatings have intrinsic limitations, particularly the risk of particulate generation resulting from coating delamination or fragmentation of large drug crystals, which may cause distal embolization and microvascular injury to non-target myocardial territories [14].

Importantly, crystalline PCB differ not only in paclitaxel morphology but also in excipient composition, a key determinant of drug adhesion, protection against wash-off during transit, and transfer efficiency. Commonly used excipients include iopromide, urea, dextran, and butyryl-tri-*n*-hexyl citrate (BTHC), each specifically engineered to minimize drug loss during delivery and optimize local drug deposition and uptake.

Over time, multiple crystalline PCB technologies have been refined and introduced into clinical practice, each characterized by a unique combination of coating architecture, excipient chemistry, and pharmacokinetic characteristics (Table 6.1).

SeQuent Please (B. Braun, Melsungen AG, Germany)

The SeQuent Please NEO PCB is coated with 3 μg/mm^2 crystalline paclitaxel using iopromide as a hydrophilic excipient (Paccocath® technology) [15]. Iopromide forms a stabilizing matrix that preserves paclitaxel integrity during device delivery and enables efficient, sustained drug transfer upon balloon inflation. Preclinical and early clinical studies demonstrated consistent antiproliferative efficacy for up to 14 days [16]. Owing to its robust clinical evidence, the SeQuent Please NEO PCB is widely regarded as the reference standard for evaluating newer DCB technologies.

IN.PACT (Medtronic, USA)

The IN.PACT technology, also adopted for the newer Prevail PCB, delivers 3.0–3.5 μg/mm^2 paclitaxel using a urea-based coating, which ensures controlled dissolution and sustained drug release.

An in vitro study demonstrated the superiority of the urea-based IN.PACT Admiral over the

Table 6.1 Summary of available drug-coated balloons in clinical practice (year 2025)

Category	Device	Company (country)	Drug/Dose (μg/mm²)	Excipient/Carrier	Coating morphology
Crystalline PCB	SeQuent please NEO	B. Braun (Germany)	Paclitaxel 3	Iopromide	Crystalline
	IN.PACT admiral	Medtronic (USA)	Paclitaxel 3.5	Urea	Crystalline
	Pantera lux	Biotronik (Germany)	Paclitaxel 3	BTHC	Crystalline
	Danubio	Minvasys (France)	Paclitaxel 2.5	BTHC	Crystalline
	Prevail	Medtronic (USA)	Paclitaxel 3.5	Urea	Crystalline
	Protégé	Wellinq (Netherlands)	Paclitaxel 3.0	PVV	Crystalline
	Agent	Boston Scientific (USA)	Paclitaxel 2.0	ATBC	Crystalline
Amorphous PCB	DIOR	Eucor (Germany)	Paclitaxel 3	Shellac	Amorphous
	Elutax	Aachen resonance (Germany)	Paclitaxel 2.2	Dextran	Microcrystalline
	RESTORE	Cardionovum (Germany)	Paclitaxel 3	SAFEPAX (ammonium salt)	Amorphous
	Essential pro	iVascular (Spain)	Paclitaxel 3	Amphiphilic excipient (80/20)	Microcrystalline
	Genoss PCB	Genoss co (South Korea)	Paclitaxel 3	Shellac + vitamin E	Amorphous
Sirolimus SCB	SeQuent	B. Braun (Germany)	Sirolimus 4	BHT	Crystalline
	Magic touch	Concept medical (USA)	Sirolimus 1.25	Phospholipid nanocarrier (Nanolute™)	Amorphous
	Selution	MedAlliance (Switzerland)	Sirolimus 1.0	Phospholipid blend + biodegradable micro-reservoir	Amorphous

ATBC acetyl tributyl citrate, *BHT* butylated hydroxytoluene, *BTHC* butyryl-tri-n-hexyl citrate, *PCB* paclitaxel-coated balloon, *PVV* Polyvinylpyrrolidone, *SCB* sirolimus-coated balloon

Lutonix PCB (polysorbate/sorbitol-based) in both drug-release kinetics and tissue paclitaxel concentration at 90 days. The urea coating achieved slow and consistent drug solubilization rate (≈7% at 24 h), whereas the polysorbate/sorbitol formulation released more than 50% of paclitaxel within the first hour. Histological analyses confirmed that urea-based coating produced sustained inhibition of VSMCs proliferation at 90 days, while the faster-dissolving polysorbate/sorbitol coating induced an early but transient antiproliferative response [13].

The Balloon Elution and Late Loss Optimization (BELLO) randomized controlled trial (RCT) compared the IN.PACT Falcon PCB (Medtronic) with the Taxus Liberté paclitaxel-eluting stent (Boston Scientific, USA) in patients with small-vessel coronary artery disease (CAD) (reference vessel diameter <2.8 mm). Among 173 patients followed for 3 years, the incidence of major adverse cardiac events (MACE) was significantly lower in the DCB group than in the drug-eluting stents (DES) group (14.4% vs. 30.4%; $p = 0.015$), with no cases of stent thrombosis or vessel occlusion [17].

Pantera Lux (Biotronik, Berlin, Germany)

The Pantera Lux PCB incorporates 3 μg/mm² of paclitaxel within a BTHC-based coating, pro-

moting rapid vascular absorption and sustained local drug retention.

In a preclinical study involving 15 young adult hybrid farm pigs, the Pantera Lux PCB demonstrated the greatest inhibition of neointimal proliferation at 28 days compared with POBA, the first generation of Elutax PCB, and the SeQuent Please NEO PCB [18].

Danubio PCB (Minvasys, Lyon, France)

The Danubio PCB is coated with 2.5 μg/mm^2 paclitaxel embedded in a BTHC lipophilic matrix.

Preclinical studies in porcine coronary arteries demonstrated significant reductions in restenosis compared with POBA, with no evidence of toxicity, fibrin deposition, or thrombus formation at 28 days.

In a RCT evaluating the Danubio PCB for side-branch dilation in bifurcation lesions, angiographic follow-up at 6 months showed excellent outcomes, with a minimal late lumen loss (LLL) (−0.04 ± 0.34 mm) and a low restenosis rate (2%) [19].

Prevail (Medtronic, USA)

The Prevail PCB delivers 3.5 μg/mm^2 paclitaxel combined with urea as hydrophilic excipient.

Urea facilitates rapid drug diffusion during balloon inflation and promotes the formation of solid-phase paclitaxel reservoirs, achieving therapeutic tissue concentrations for more than 90 days [20]. In a recent head-to-head comparison, the urea-based Prevail PCB and the iopromide-based SeQuent Please NEO PCB demonstrated comparable efficacy and safety at 1-year follow-up, with a cumulative target lesion failure (TLF) rate of 8.1% in both groups (adjusted HR 0.90; 95% CI 0.27–3.00) [21].

Protégé (Wellinq, The Netherlands, and Translumina, India)

The Protégé PCB is coated with 3.0 μg/mm^2 paclitaxel applied over a polyvinylpyrrolidone matrix, which acts as a hydrophilic sponge allowing controlled, pressure-dependent drug release during inflation. A distinctive feature of this platform is its availability in both compliant and noncompliant configurations.

Clinical outcomes from the PEARL Registry (n = 513 patients) demonstrated favorable safety and efficacy, with MACE rates of 17.1% in in-stent restenosis (ISR) and 9.7% in de novo lesions, and TLR rates of 11.7% and 2.9%, respectively. When compared with the MagicTouch sirolimus-coated balloon (SCB), the Protégé PCB achieved comparable results across diverse lesion subsets [22].

Agent (Boston Scientific, USA)

The Agent PCB features a low-dose crystalline paclitaxel coating (2 μg/mm^2) combined with acetyl tributyl citrate (ATBC) as excipient. ATBC enhances tissue penetration, improves coating flexibility, and stabilizes the drug layer, thereby facilitating efficient drug transfer and durable retention within the target vessel segment. In preclinical studies, the Agent PCB achieved higher acute tissue paclitaxel concentrations compared with the MagicTouch SCB, SeQuent Please NEO PCB, and Selution SCB platforms.

From a clinical perspective, long-term outcomes in patients with DES-ISR treated with the Agent PCB or SeQuent Please NEO PCB showed no significant difference in target lesion revascularization (TLR) at 7 years, confirming comparable long-term efficacy [23].

The pivotal AGENT IDE RCT, conducted in collaboration with the U.S. Food and Drug Administration (FDA), enrolled 600 patients with ISR across 40 centers in the United States.

At 1-year follow-up, TLF occurred in 17.9% of patients treated with the AGENT DCB versus 28.6% in the uncoated balloon group (HR 0.59; 95% CI 0.42–0.84; p = 0.003), with significantly lower rates of TLR and target vessel-related myocardial infarction (MI) [24]. Following these results, the Agent PCB became the first drug-coated balloon approved in the United States for the treatment of ISR.

6.2.2.2 Noncrystalline and Microcrystalline Paclitaxel-Coated Balloons

Amorphous (noncrystalline) paclitaxel coatings provide excellent stability during device tracking and allow efficient drug transfer to the vessel wall. However, compared with crystalline formu-

lations, amorphous coatings typically achieve shorter tissue retention at therapeutic concentrations. Over time, continuous technological refinements have led to next-generation noncrystalline PCB with prolonged drug persistence at the target site and consistent clinical efficacy across diverse subsets of CAD.

DIOR (Eucor GmbH, Bonn, Germany)
The DIOR PCB was the first noncrystalline PCB introduced into clinical practice. It featured a homogeneous, durable bioshell coating composed of a 1:1 mixture of paclitaxel (3 μg/mm^2) and shellac, specifically designed to protect the drug from mechanical abrasion and minimize premature wash-off during delivery.

In a preclinical study involving 33 pigs, the DIOR PCB achieved a significantly larger lumen area and reduced neointimal formation compared with POBA [25].

Clinically, the DIOR PCB demonstrated acceptable performance in both ISR and small-vessel CAD [26]. However, it proved inferior to the SeQuent Please PCB, showing a higher 3-year TLR rate (22.6% vs. 4.7%), [27] and was also outperformed by the Taxus DES in the PICCOLETO trial, which was consequently terminated early. These results were likely attributable to low tissue drug concentrations and suboptimal lesion preparation, and this device was recalled from the market due to lower efficacy [28].

Elutax (Aachen Resonance, Germany)
The Elutax PCB is coated with 2.2 μg/mm^2 of paclitaxel in a microcrystalline form and incorporates 0.7 μg/mm^2 of dextran as a hydrophilic excipient. Dextran functions as a natural hydrogel, protecting the drug during delivery and ensuring minimal drug loss (<5%) before reaching the target lesion by providing mechanical protection against friction both outside the body and within the vessel.

In the multicenter randomized PICCOLETO II trial (Drug-Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment), which enrolled patients with de novo small-vessel disease (SVD), the Elutax DCB demonstrated superior angiographic efficacy, achieving significantly lower LLL compared with everolimus-eluting stents, while maintaining comparable or even improved clinical outcomes at both 1- and 3-year follow-up [29, 30].

RESTORE (Cardionovum, Bonn, Germany)
The RESTORE PCB is coated with 3 μg/mm^2 of paclitaxel and incorporates the proprietary SAFEPAX® technology, a homogeneous, noncrystalline amorphous coating composed of paclitaxel and an ammonium salt excipient. This formulation minimizes drug wash-off, prevents crystallization, and reduces the risk of distal particulate embolization, while ensuring uniform drug distribution and stable delivery during balloon inflation.

In the RESTORE ISR China trial, which randomized 240 patients with DES-ISR to RESTORE PCB or SeQuent Please NEO PCB, LLL at 9 months and TLF at 1 year were comparable between groups (13.3% vs. 12.6%, $p = 0.87$) [31].

Similarly, in the RESTORE SVD China trial, the RESTORE PCB achieved outcomes comparable to second-generation DES at 2 years, with low revascularization rates and no late catch-up [32].

Essential Pro (iVascular, Spain)
The Essential Pro PCB delivers 3 μg/mm^2 of paclitaxel using an ultrasonic nanodrop deposition technique that creates a multilayer, ultrathin microcrystalline coating combined with a biocompatible amphiphilic excipient. This advanced process ensures homogeneous drug distribution, enhances adhesion and transfer efficiency, and promotes effective vessel wall uptake, resulting in consistent and durable antiproliferative efficacy. The Essential Pro DCB has shown favorable outcomes in both SVD and ISR studies [33].

Genoss PCB (GENOSS CO LTD, South Korea)
The Genoss PCB incorporates 3 μg/mm^2 of paclitaxel on the balloon surface and employs a novel excipient blend of shellac and vitamin E. Vitamin E acts as a bioactive antioxidant, reducing the expression of plasminogen activator inhibitor-1, a mediator of vascular injury following angioplasty.

In a RCT comparing the Genoss PCB with the SeQuent Please NEO PCB in patients with de novo CAD, both devices demonstrated comparable angiographic and clinical outcomes. Late lumen enlargement (44.7% vs. 42.7%; $p = 0.903$) and binary restenosis rates (3.2% vs. 6.7%; $p = 0.442$) were similar between groups. Likewise, 12-month TVF rates did not differ significantly (3.0% vs. 4.3%; $p = 0.921$) [34].

6.3 Sirolimus-Coated Balloons

SCB were developed to overcome key limitations of PCB, particularly the narrow therapeutic window and the risk of distal embolization with the crystalline formulations [12].

Sirolimus exerts its antiproliferative effect through a distinct molecular pathway and has a broader therapeutic range (1–7 μg/mm^2). It inhibits the mammalian target of rapamycin (mTOR), a serine/threonine kinase that regulates cell growth, proliferation, and survival. By binding to the cytosolic protein FKBP12, sirolimus forms a complex that blocks mTOR activity, inducing cell-cycle arrest in the G_0 phase and inhibiting the proliferation of both VSMCs and endothelial cells. Through this dual mechanism, sirolimus promotes controlled vascular healing and effectively suppresses neointimal hyperplasia, ensuring long-term vessel patency [35].

Nevertheless, the pharmacokinetic limitations of sirolimus, mainly its lower lipophilicity, which leads to limited tissue uptake and short retention time, initially hindered the development of SCB technology. Modern sirolimus-based platforms have since integrated controlled-release carrier systems and micro- or nanotechnology-based excipients to achieve sustained drug delivery and maintain therapeutic tissue concentrations over time.

Currently, multiple SCB technologies are available in clinical practice, each distinguished by specific coating matrices, excipient compositions, and drug-release kinetics, reflecting continuous innovation in sirolimus delivery systems (Table 6.1).

6.3.1 Crystalline Sirolimus-Coated Balloon

SeQuent SCB (B. Braun, Melsungen, Germany)
The SeQuent SCB (B. Braun, Melsungen, Germany) features a crystalline sirolimus coating (4 μg/mm^2) combined with butylated hydroxytoluene (BHT) as an excipient. The incorporation of BHT enhances sirolimus stability and prolongs vascular tissue retention, maintaining approximately 50% of the initial vessel wall concentration at 1 month [36].

In a randomized, multicenter first-in-human trial, Ali et al. evaluated 50 patients with DES-ISR treated with either the SeQuent SCB or the SeQuent Please Neo PCB. Baseline angiographic parameters were similar between groups. At 6 months, in-segment LLL was 0.21 ± 0.54 mm with PCB and 0.17 ± 0.55 mm with SCB, while 12-month clinical outcomes did not differ significantly, demonstrating comparable efficacy and safety between the two platforms [37].

In a subsequent randomized controlled trial, Ahmad et al. compared the SeQuent SCB with the SeQuent Please NEO PCB in 70 patients with de novo CAD. At 6 months, angiographic findings were again comparable (LLL: 0.10 ± 0.32 mm with SCB vs. 0.01 ± 0.33 mm with PCB; mean difference 0.08 mm, 95% CI −0.07 to 0.24). Although late lumen enlargement was observed more frequently after PCB treatment (60% vs. 32%; $p = 0.019$), MACE rates at 12 months were similar [38].

6.3.2 Noncrystalline Sirolimus-Coated Balloons

MagicTouch (Concept Medical, Tampa, USA)
The MagicTouch SCB is a nanotechnology-based SCB that incorporates submicron sirolimus particles encapsulated within phospholipid-based nanocarriers, uniformly applied to the balloon surface using an electrostatic spray-coating process. This Nanolute™ technology enables efficient and sustained drug transfer at a low sirolimus dose density (1.25 μg/mm^2). The

phospholipid carrier, composed of two lipophilic tails and one hydrophilic head, provides a stable amphiphilic matrix that enhances sirolimus solubility, promotes diffusion into deeper arterial layers, and minimizes particulate loss. This configuration ensures complete surface coverage, minimal drug loss (<10%), and rapid release kinetics, with approximately 56% of sirolimus released within 40–60 s of balloon inflation. Drug persistence in the vessel wall for 15–30 days ensures therapeutic tissue levels during the critical vascular healing phase [39].

In a prospective, multicenter RCT trial including 121 patients with small-vessel CAD, the MagicTouch SCB demonstrated inferior angiographic performance compared with the SeQuent Please Neo PCB, showing a lower net lumen gain (0.25 ± 0.40 mm vs. 0.48 ± 0.37 mm; *p* for noninferiority = 0.173). However, safety and clinical outcomes at 6 months were comparable between the two treatment groups [40].

In the EASTBOURNE Registry, which enrolled 2123 patients across Europe and Asia, the MagicTouch SCB demonstrated excellent real-world performance. At 12 months, the rates of TLR and MACE were 5.9% and 9.9%, respectively, with a low incidence of bailout stenting (7.7%) and no thrombotic occlusions [41]. At 2-year follow-up, available for 90% of patients (*n* = 1907 patients), the cumulative incidence of clinically indicated TLR was 7%, with only 1% of new events between years 1 and 2. MACE increased modestly to 11.2%, mainly due to small rises in cardiac death (1.6%), spontaneous MI (4.1%), and target vessel revascularization (6.8%), while all-cause mortality (5.3%) and Bleeding Academic Research Consortium 2–5 bleeding (1.3%) remained low [42].

Selution (MedAlliance, Nyon, Switzerland, and Cordis, USA)

The Selution is a SCB characterized by microreservoir technology that incorporates sirolimus within a biodegradable polymer carrier. This platform features two key components: a phospholipid blend that encapsulates and protects the sirolimus micro-reservoirs (dose density: 1 μg/mm^2), enhancing drug stability and transfer efficiency during balloon delivery; spherical microreservoirs (approximately 4 μm in diameter) composed of a biodegradable polymer matrix, enabling controlled and sustained drug elution and maintaining therapeutic sirolimus concentrations within the target vessel wall over time.

Through this dual-layer design, the Selution SCB achieves prolonged and homogeneous sirolimus release, mimicking the kinetics of drug-eluting stents while preserving the vessel's native anatomy.

In the SELUTION DeNovo RCT, 3341 patients undergoing PCI were assigned to Selution SCB-based PCI or a DES strategy. At 1 year, TVF occurred in 5.3% of SCB-treated versus 4.4% of DES-treated patients, meeting the noninferiority margin. Rates of cardiac death, target vessel MI, and clinically driven TLR were similarly low across both groups, confirming comparable short-term safety and efficacy [43].

Similarly, in the SELUTION4ISR trial, which enrolled 418 patients with in-stent restenosis, SCB treatment was noninferior to the standard of care (DES or POBA), with TVF rates of 15.2% vs. 13.5%, and no significant differences in cardiac death, MI, or TLR [44].

6.4 Preclinical Evidence

Aihara and colleagues conducted a preclinical investigation in healthy iliac arteries of 18 rabbits to compare the histological and biological characteristics of the Agent PCB, the SeQuent Please NEO PCB, and the MagicTouch SCB.

At the level of the treated segment, both the Agent PCB and the SeQuent Please NEO PCB demonstrated significantly decrease medial VSMCs scores, the primary efficacy endpoint, compared with the MagicTouch SCB (4.0 [3.6–4.0] vs. 3.7 [3.7–4.0] vs. 2.2 [2.0–2.4]). Conversely, drug concentrations in distal skeletal muscle were highest for the MagicTouch SCB, followed by SeQuent Please NEO PCB and the Agent PCB (28.07 [13.19–52.46] ng/mg vs. 0.66 [0.22–3.76] ng/mg vs. 0.25 [0.04–3.23] ng/mg, respectively).

These findings suggest that PCB may achieve higher local efficacy while maintaining lower distal drug dissemination compared with SCB, with comparable results between the Agent PCB and the SeQuent Please NEO PCB [45].

However, it is important to note that the rabbit model provides limited translational value for human coronary applications, as its vascular anatomy and pharmacodynamic response differ substantially from those observed in porcine models, which are more physiologically representative of human coronary physiology [46].

In a subsequent study, Kawai et al. evaluated 28 coronary arteries from 10 pigs treated with three different DCB, the MagicTouch SCB, the Selution SCB, and the Agent PCB, or with POBA, followed by 28-day histopathologic evaluation.

Compared with the Agent PCB, both the MagicTouch SCB and the Selution SCB exhibited less medial SMC loss. Notably, PCB-treated arteries were the only group with histologic evidence of myocyte necrosis and scarring in 21% of sections, whereas no such findings were observed with SCB devices ($p < 0.01$). Of interest, the incidence of downstream embolization was lower with the MagicTouch SCB (15%) compared to the Selution SCB (25%) and the Agent PCB (36%) [47].

A more recent investigation by Finn and colleagues compared the pharmacokinetic profiles of Selution SCB, MagicTouch SCB, and Xience DES in 36 animal porcine models with long-term follow-up. From an efficacy standpoint, Selution SCB and Xience DES demonstrated similar levels of tissue drug concentration, both within the therapeutic range over time. In contrast, MagicTouch SCB showed a further decline in tissue concentration, falling below the therapeutic threshold at 90 days. If higher these tissue levels after the first weeks from the intervention are associated with improved clinical outcomes, is unclear yet. Regarding safety evaluation, Xience DES displayed the lowest drug levels in downstream myocardium, while the MagicTouch SCB exhibited higher distal concentrations than Selution SCB [48].

6.5 Clinical Evidence

Few clinical studies have evaluated the impact of different drug types and coating technologies among DCB platforms on coronary microvascular function. In vivo assessment of drug-induced microembolization remains challenging, as direct measurement of distal particulate embolization is not feasible during PCI.

A promising surrogate parameter is angiography-derived microcirculatory resistance (AMR), a non-wire-based index calculated from angiography-derived quantitative flow ratio (QFR) and estimated flow velocity using Murray's law. AMR has been shown to correlate strongly with the invasive index of microcirculatory resistance (IMR). Changes in AMR (ΔAMR), defined as the difference between post- and pre-procedural values, can therefore serve as a surrogate marker of microvascular injury or distal embolization occurring during DCB angioplasty.

A subanalysis of the TRANSFORM I trial (Treatment of Small Coronary Vessels: MagicTouch Sirolimus-Coated Balloon) investigated the acute effect of DCB angioplasty on coronary microcirculation. This study enrolled 121 patients (126 vessels) with either acute or chronic coronary syndromes and at least one de novo small-vessel lesion. Patients were randomized 1:1 to receive either the MagicTouch SCB or the SeQuent Please NEO PCB. In this subanalysis, AMR was measured at baseline and immediately after DCB inflation by an independent core laboratory. Coronary microvascular dysfunction (CMD) was defined as AMR ≥2.5 mmHg·s/cm.

In the SCB group, the median AMR increased modestly after the procedure (2.03 [1.58–2.42] → 2.21 [1.78–2.53] mmHg·s/cm; $p = 0.03$), without a significant change in the proportion of vessels with CMD (22.0% → 32.2%; $p = 0.19$). In contrast, the PCB group showed a greater post-procedural AMR rise (2.22 [1.66–2.53] → 2.45 [1.93–2.96] mmHg·s/cm; $p = 0.003$) and a significant increase in CMD prevalence (27.1% → 47.5%; $p = 0.046$) [49]. These findings suggest that sirolimus-coated nanocarrier platforms may induce less

microvascular dysfunction than crystalline paclitaxel-based coatings, potentially due to lower particulate release during inflation.

An important post hoc analysis from the PICCOLETO VI study [50] further explored the relationship between coating morphology and microvascular function.

This study included 224 lesions treated with either PCB or SCB and stratified according to coating structure (crystalline vs. amorphous). Overall, AMR increased significantly from baseline to post-procedure (mean ΔAMR = 0.69 ± 0.93 mmHg·s/cm).

Lesions treated with crystalline-coated DCB showed a greater ΔAMR compared with amorphous-coated DCB (0.92 ± 0.99 vs. 0.53 ± 0.98 mmHg·s/cm; p = 0.033) (Fig. 6.1), whereas no significant difference was observed between paclitaxel- and sirolimus-based balloons (0.78 ± 1.35 vs. 0.58 ± 1.07 mmHg·s/cm; p = 0.229) (Fezzi, Gurgoglione, Cortese et al., submitted, to be updated later).

These results support the hypothesis that coating morphology, rather than the specific antiproliferative drug, plays a key role in determining the degree of microvascular injury through distal particulate embolization.

Whether these microvascular differences translate into long-term clinical outcomes still remains uncertain. The only available clinical data derive from a study by Wang et al., which evaluated 108 patients undergoing DCB angioplasty with 1-year follow-up angiography. In this study target-vessel restenosis (>50% diameter stenosis) occurred in 35% of patients. Notably, post-procedural AMR emerged as an independent predictor of restenosis (adjusted OR = 22.8; 95% CI: 1.58–328.11; p = 0.022) [51].

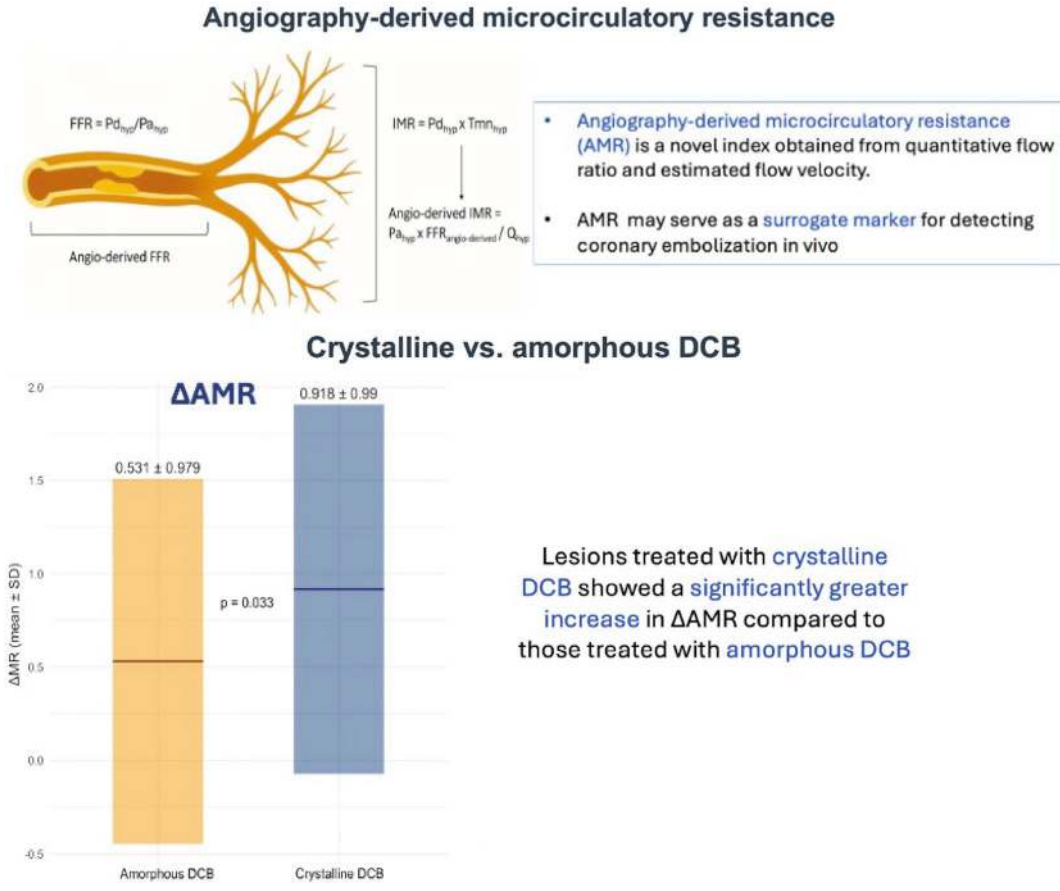


Fig. 6.1 Crystalline vs. amorphous DCB and effects on microvascular resistance after PCI

These findings highlight the need for further mechanistic investigations integrating invasive IMR assessments to elucidate the interplay between drug type, coating technology, and microvascular function, and to define their prognostic significance in contemporary DCB therapy. In conclusion, it is not clear if it is appropriate to describe a class effect among DCB, with several devices currently in the European market (so far, not yet in the American one) warranting a good quality standard [52,53]. Only direct comparisons among different devices, possibly with clinical measures of outcome, can depict meaningful differences. 52 Gurgoglione FL, Cortese B. Different Drugs, Similar Outcomes? Challenging the No-Class-Effect Motto of Drug-Coated Balloon in Coronary Artery Disease. J Soc Cardiovasc Angiogr Interv. 2026 Apr 16;5(6):105374. doi: 10.1016/j.jscai.2026.105374. PMID: 42516851; PMCID: PMC13404013. 53 Cortese B, Murad E. Paclitaxel Noninferior to Paclitaxel: Registry-Scale Evidence for an Urea-Excipient Drug-Coated Balloon in a Real World Population: A Commentary on the SCAAR Nationwide Comparative Registry Analysis. J Am Heart Assoc. 2026 Jun 2;15(11):e051188. doi: 10.1161/JAHA.126.051188. Epub 2026 May 29. PMID: 42216286; PMCID: PMC13315128.

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7 Newer Drug Transfer Technologies for DCB: TransferTech Nanotechnology for Paclitaxel Delivery

Lluís Duocastella Codina, María Molina Crisol, and Alex Gómez Castel

7.1 TransferTech Nanotechnology

7.1.1 Formulation

In this TransferTech nanotechnology, there are two components: the drug paclitaxel, and a proprietary excipient water reduced ester.

The presence of an excipient plays a central role during the navigation and in the transfer of paclitaxel into the vessel wall from the surface of a balloon. The excipient needs to be lipophilic in order to retain the paclitaxel on the balloon, but it is also important that it is soluble in water to help paclitaxel transfer and diffuse through the vessel wall. The excipient should have both characteristics: be amphiphilic. Essential pro is the only DCB with an amphiphilic excipient, a water reduced ester.

The hydrocarbon chains of this excipient create a sufficiently lipophilic environment for paclitaxel, which, due to its molecular structure, is also lipophilic and thus dissolves in the excipient. Additionally, this composition makes the coating lipophilic, preventing its detachment into the bloodstream or other hydrophilic environments. Consequently, when the blood flow contacts the coating during navigation, it cannot dissolve or extract paclitaxel, resulting in minimal losses. Furthermore, the lipophilic nature of the excipients enhances their interaction with the tissue during transfer, facilitating paclitaxel absorption. Therefore, the excipients exhibit a synergistic effect that enhances the therapeutic efficacy of paclitaxel.

When the balloon catheter contacts the blood flow, a slight solubilization or wetting effect of the coating occurs, leading to a gel-like appearance. In this context, the terms "gel effect" or "gel-type coating" may be used. *The gel-type coating minimizes and can even eliminate the possibility of particle detachment and improves drug transfer through the tissue*. This proprietary excipient promotes the formation of the gel effect, reducing navigation losses and enhancing tissue transfer.

Regarding the drug, paclitaxel has a main advantage over sirolimus in drug-coated balloons, thanks to its high lipophilicity. This characteristic allows for a faster and more efficient transfer of the drug to the arterial wall. Due to its highly lipophilic nature, paclitaxel can quickly penetrate arterial tissues, facilitating its therapeutic action within a limited timeframe.

As sirolimus is less lipophilic, it hampers its direct and rapid transfer to the arterial wall. To enhance its effectiveness, sirolimus needs to be

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encapsulated in lipophilic compounds, adding an additional layer of complexity to the drug formulation and transfer process.

7.1.2 Spray Nanotechnology and Ultra-Thin Multi-Layer Coating

The drug formulation of Essential pro is spread on the balloon by ultrasound spray pulse. The balloon surface is coated with multiple and independent nanodrop layers. This nanotechnology controls the surface finishing of the drug coating also known as texturing. Textures can range from amorphous to crystalline, or smooth to rough.

The coating obtained by spray is uniform, homogeneous, and highly resistant due to the good adhesion of the composition of the coating to the balloon material. The good adhesion also makes that only a slight solubilization of the coating is observed during navigation, the so-called gel effect, i.e., losses during navigation are very low, and excellent drug transfer to the arterial wall is obtained.

The advantage of a multi-layer coating versus a single-layer coating is the integrity of the coating in view of the handling and navigation. In addition, coating adhesion to the balloon is better in the case of a multi-layer coating, which reduces delaminations during handling and prevents formation of micropores in the coating. Therefore, the multi-layer coating will have fewer losses during navigation than the single-layer coating.

This proprietary ultrasonic spray coating offers significant process flexibility and reliability in creating and reproducing various textures. Key parameters such as flow rate, ultrasonic power, and application distance are essential for achieving the desired drug coating texture. Unlike conventional spray techniques used by other coating companies, ultrasonic nozzles do not rely on pressure to shear the solution into droplets. Instead, high-frequency vibrations create droplets with a very narrow size distribution. Air shaping guides the droplets to the balloon to form the drug solution coating (Fig. 7.1).

Other factors, such as solvent, concentration, and rotation, contribute as well to the texture of the coating.

7.1.3 Dry Off Technology

The texture obtained depends on the droplet size, resulting in crystalline or amorphous coatings.

This micro-crystalline matrix obtains droplets by drying slowly, resulting in crystalline coatings. It is important to have the drug in a crystalline state, as this will affect its residence time in the arterial wall. The physical form of paclitaxel



Fig. 7.1 TransferTech nanotechnology

impacts its solubility, and consequently, its release and retention in tissues. In its crystalline form, paclitaxel tends to dissolve more slowly due to its ordered and stable structure. This can result in a prolonged release of the drug, potentially increasing its residence time in the arterial wall [1].

In contrast, the amorphous form of paclitaxel has a disordered and less stable structure, generally resulting in higher solubility and release rates. This higher solubility can be responsible for reduced efficacy, as the drug concentration decreases over time and may be limited in its function of inhibiting arterial smooth muscle cells.

The majority of DCB manufacturers use PTX as drug due to its properties, but not all DCB are designed equally, nor are they equivalent. Beyond the differences related to the balloon platforms, the technique of impregnation, the physicochemical structure of PTX and its combination with the excipient, are differentiating elements that could be related to the clinical effectiveness.

TransferTech nanotechnology, such unique and innovative technology, provides with a flexible coating that adapts to the balloon movement. Essential pro provides a minimum drug loss during navigation, high drug transfer within 30–60 s and long retention time according to this technology due to the excellent properties of the coating and its composition (Fig. 7.2).

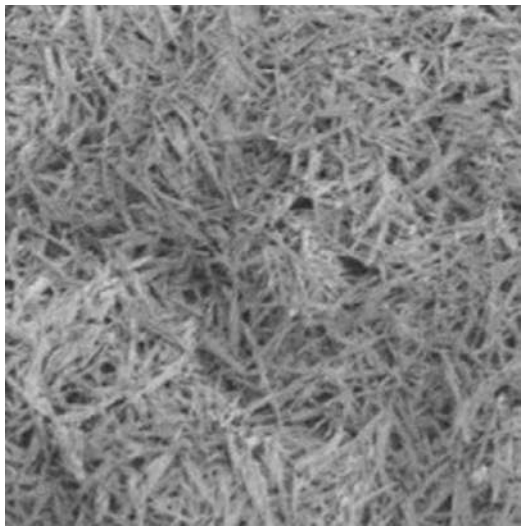


Fig. 7.2 Essential pro microcrystals with SEM (Scanning Electron Microscope)

7.2 Clinical Evidence

7.2.1 Essential DCB in Small Vessels: Percutaneous Coronary Intervention for Treating De Novo Lesions in Small Coronary Vessels: Initial Experience with the Essential Paclitaxel-Coated Balloon

Prospective, multicenter, observational study designed to assess short and medium-term outcomes with Essential pro[1] for treating de novo lesions in small coronary vessels (with a diameter <2.5 mm). The study enrolled 71 patients with de novo coronary lesions in small vessels, with clinical follow-up at 12 months [2].

The primary objective was to evaluate target lesion failure (TLF) at 12 months, defined as cardiac death, myocardial infarction related to the treated vessel, and target lesion revascularization (TLR). Secondary endpoints included target vessel failure (TVF) and Major Adverse Cardiac Events (MACE) evaluated at 12 months.

The mean age of the patients was 66 ± 11 years. Among the patients, 56% were diabetic, and 70% had an acute coronary syndrome as the indication for coronary revascularization. Predilatation was performed in 85.9% of the cases. Angiographic success, defined as achieving satisfactory dilation of the lesion without significant residual stenosis or complications, was achieved in 97.2% of the cases. Bail-out stenting was required in only nine cases (12.7%) [2].

At the 12-month follow-up, the incidence of TLF was 4.2%, indicating a favorable safety profile for this technology. This incidence of TLF suggests that the device is effective in minimizing adverse cardiac events related to the target lesion. The rates of TVF and MACE were 4.2% and 9.9%, respectively. These outcomes reflect a low incidence of complications and adverse events associated with the procedure and the device.

[1]The study was conducted using the Essential DCB, the predecessor of the Essential pro but both maintaining the same nanotechnology TransferTech.

The results from the ESSENTIAL study demonstrate that the use of Essential pro for the treatment of de novo coronary lesions in small vessels is both safe and effective. The low rates at 12 months suggest that this device is a reliable alternative especially in the context of small vessel disease where options can be limited.

7.2.2 Essential DCB in In-Stent Restenosis: Angiography and Optical Coherence Tomography Assessment of the Drug-Coated Balloon Essential for the Treatment of In-Stent Restenosis

Prospective, multicenter, single-arm clinical study aimed at evaluating the efficacy of Essential pro[1] for the treatment of significant ISR. The study's primary endpoints involved quantitative coronary angiography (QCA) and optical coherence tomography (OCT) assessments, with follow-ups conducted at 6, 12, and 24 months [3].

The study enrolled 33 patients who met specific QCA and OCT criteria for ISR. These criteria ensured that the sample size was adequate for robust statistical analysis and allowed for meaningful cross-comparisons with other studies.

The primary objective was to evaluate the maximum stenosis area by OCT at 6 months. Secondary endpoints included late lumen loss (LLL) at 6 months and target lesion failure (TLF) rates at 6, 12, and 24 months. TLF was defined as the composite outcome of cardiac death, myocardial infarction related to the target vessel, and target lesion revascularization (TLR) [3].

Angiographic success was achieved in 31 out of 33 patients (93.9%). Stent implantation was necessary in only two patients due to suboptimal angiographic results after balloon dilation. At the 6-month follow-up, the mean maximum stenosis area was low at 51 ± 13%, comparable to published results of other devices. Segmental LLL was low at 0.25 ± 0.43 mm, with binary restenosis observed in only two patients. At 12 months, the TLF rate was 13.3% maintained at 24 months. Importantly, all TLF events were attributed to TLR, with no instances of cardiac death, myocardial infarction, or thrombosis reported. These results demonstrate that Essential pro is effective in treating ISR as assessed by OCT and QCA, with outcomes comparable to other devices. Clinical efficacy remained favorable and sustained in the long term.

7.2.3 Essential pro DCB in In-Stent Restenosis: Safety and Efficacy of the Essential pro Paclitaxel Drug-Eluting Balloon for the Treatment of Coronary In-Stent Restenosis

Prospective, single-center clinical investigation aimed at evaluating the safety and efficacy of Essential pro in patients with ISR. This study enrolled 160 consecutive patients, accounting for 206 treated lesions, and the follow-up period extended to a maximum of 768 days [4].

The primary objectives were to assess the safety and efficacy of the new-generation Essential pro DCB for the treatment of ISR. Key endpoints included myocardial infarction, target lesion revascularization (TLR), and target vessel revascularization (TVR).

The cohort had a mean age of 71.4 ± 14.9 years, with 15.5% women and 35.5% diabetic patients. Acute coronary syndrome was present in 53.3% of the patients. The treated vessel's average diameter was 3.10 ± 0.7 mm. Predilatation was performed in 98% of the lesions, predominantly using non-compliant balloons [4].

At the end of the procedure, 98.5% of patients achieved TIMI flow grade 3, residual stenosis <30% in 96.6% and bail-out stenting was required only in 4.8% of the procedures. During the follow-up period, the mortality rate was zero. The incidences of myocardial infarction and TLR were 5.4% and 8.4%, respectively. The study demonstrated a high success rate and a low incidence of adverse clinical outcomes, underscoring the safety and efficacy of the Essential pro DCB for treating ISR.

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8 Advancement of Nanotechnology for Drug-Coated Balloons: Challenges and Future Considerations

Prakash Sojitra, Frank Proch, Marwan Berrada-Sounni, and Vinod Labhasetwar

8.1 Introduction

Nanotechnology is the study and manipulation of matter at the atomic, molecular, and supramolecular levels, utilizing dimensions up to 300 nm for drug delivery applications [1, 2]. To offer a sense of the dimensions involved, a human hair cross-section diameter is approximately 80,000 nm, a red blood cell is around 7000 nm, and the smallest bacteria are about 200 nm in diameter; moreover, biological molecules far smaller than the bacterial scale are commonly encountered. Materials at the nanometer scale often exhibit unexpected size- and shape-dependent properties that significantly depart from their bulk characteristics. Such properties can be exploited in the design and production of novel structures, devices, and systems. Nanotechnology is widely regarded as a promising platform to develop next-generation drug-coated balloons (DCB) with enhanced performance and efficacy [3]. Due to various challenges to retain drugs in the encapsulated form, coating them on the inflatable part of the catheter, and delivering them in nanoparticle form, very few efforts have been successful in utilizing nanotechnology at the clinical stage with notable preclinical or biological efficacy [4, 5].

DCB enhance the delivery of antiproliferative or anti-inflammatory drugs, thereby reducing both short- and long-term complications, which may originate from the previous stent implantation or restenosis lesions. DCB are categorized into three types: DCB coated with (i) micron-sized particles (mDCB), (ii) nanometer-sized particles (nDCB), and (iii) drug crystals. Originating from modifications of drug-eluting stents (DES), DCB enable local, controlled, and sustained drug delivery from the balloon surface [3]. To date, primarily two drugs, namely sirolimus and paclitaxel, have been studied on DCB due to their broad clinical acceptance in treating proliferative vascular diseases. However, paclitaxel-coated balloons (PCBs) are intermittently debatable, mainly in below-the-knee indications [6–8]. PCBs have demonstrated a positive remodeling effect, as evidenced by late lumen increase following DCB-only therapy [9]. Furthermore, paclitaxel is a highly lipophilic agent that facilitates tissue uptake and maintains a sustained biological effect at minimal doses [10]. Various literature in the field focuses on the lipophilicity differences between sirolimus and paclitaxel, which are associated with altered pharmacokinetic profiles and tissue retention [11]. These differences are attributed to their dif-

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ferent physical states (crystalline and amorphous) combined with various carriers or binders. It is believed that the fate of DCB lies in a high in-tissue pharmacokinetic profile, less particulate matter, and acute drug delivery with minimum drug loss during transit. On the other hand, sirolimus-coated balloons are relatively new technologies, e.g., MagicTouch (nDCB) utilizes nanocarriers as liposomes [5], Virtue (nDCB) with nanoparticles and cytoprotectants [12], Mozaic SEB (nDCB) utilizes solid lipid nanosphere [13], and Selution SLR (mDCB) utilizes microspheres [14]. Most recently, a new sirolimus and paclitaxel-coated balloon (nDCB) was studied, where the drug delivery vehicle is PLGA surface-functionalized nanoparticles, combined with sirolimus and paclitaxel [15]. Several nanoparticle technologies for DCB are under development (Table 8.1).

The advent of nanotechnology has improved the efficiency of drug release and transfer to the arterial wall through nDCB. Various nanomaterials, such as fluorescent nanoparticles [16], polymeric nanoparticles (covalent conjugated or encapsulated), nano-shells (i.e., quantum dots), nanocrystals, nano-emulsions, and liposomes, facilitate efficient drug transport, drug depot, and sustained release in various medical applications. The sustained release profile can be further tailored from weeks to months, and it is specific to the clinical indication.

nDCB offers numerous advantages over traditional micron-sized particle drug delivery. They can achieve better site-specific drug delivery for therapeutic requirements, minimize harmful side effects, and maximize local efficacy. nDCB can also deliver high-potency therapeutics and obtain favorable pharmacokinetic profiles [5, 17]. These features make nDCB a promising platform for various vascular and non-vascular interventions. For example, nanoparticle sirolimus nDCB (MagicTouch) demonstrated less medial injury and fewer downstream effects than microparticles [18]. In PAD, slow-flow is associated with lower wound healing and a higher amputation-free rate [19]. Therefore, utilization of nanotechnology could provide more clinical benefits. From a researcher's perspective, designing nDCB is relatively challenging and needs unique skills beyond chemistry to overcome manufacturing and regulatory challenges.

This chapter offers a perspective on the formulation design, clinical translation, regulatory challenges, and future role of nanotechnology in DCB, with a focus on sirolimus and paclitaxel. It examines the risk–benefit landscape using the latest clinical and preclinical evidence.

8.2 Drug Release Mechanism and Pharmacokinetics

DCB offer an alternative method compared to DES for drug delivery, facilitating sufficient drug transfer through a single balloon inflation into the vessel wall. The primary mechanism of drug transfer involves the selective detachment of a dry drug coating from the balloon surface to the luminal vessel wall during inflation, thereby minimizing downstream particle embolization and

Table 8.1 nDCB with various nanotechnology principles

Product/study	Drug	Carrier	Dose	PK	Regulatory
MagicTouch	SRL	Phospholipid	1.27 μg/mm^2	Sustained, deep	CE, FDA IDE
NanoPac	PTX	Phospholipid	2.50 μg/mm^2	High retention	N/A
SirPlux Duo	SRL + PTX	Functionalized PLGA	1.5 μg/mm^2	Synergistic	N/A
Quercetin NP	Quercetin	PLGA	Unknown	Sustained	N/A
Mozaic SEB	SRL	Solid lipid NP	3 μg/mm2	Sustained	CE Mark
Virtue	SRL	Liquid	3 mg	Sustained	CE, FDA IDE
Luminir	PTX	Water reduced amphiphilic	3 μg/mm2	Sustained	CE

PTX Paclitaxel, *SRL* Sirolimus

facilitating tissue uptake during a single inflation event.

The model of drug transfer from balloon to arterial wall indicates that increasing the coating surface area significantly enhances drug transfer. This occurs even without changes in medial volume, tissue thickness, or coating type, whereas increases in drug-to-excipient ratio and excipient type have negligible effects on transfer kinetics and residual drug fraction [20].

Smaller-sized spherical nanoparticles have a larger surface-to-volume ratio, and hence, the same weight of nanoparticles can cover a larger area, ultimately resulting in better biodistribution. Spherical particles transfer, diffuse, and eliminate more easily than crystal or rod-shaped particles [21], which supports an optimized absorption, distribution, metabolism, and excretion (ADME) profile. Smoother surface and lower inter-particle friction make the spherical shape more dynamic and transferable. Crystal-shaped particles, particularly those with irregular shapes such as needles, dumbbells, or plate-like shapes, tend to have rougher surfaces and more points of contact, which increases friction and leads to agglomeration. On the nDCB platform, the tissue distribution of nanoparticles is not limited to target vessel contact only, but can also be distributed proximally and distally to the treated (drug-balloon contact area) sections due to its higher diffusion properties, which could be an advantage in edge restenosis treatment.

The mechanical release of the drug coating during inflation exposes the physical drug formulation to the vessel wall, ultimately resulting in pharmacokinetic (PK) values. It is presumed that a higher and longer pk is better, but when nano is compared with micro, a higher or longer pk does not always mean better [20].

Example In the case of an anti-malarial or antibiotic drug regimen, any drug taken longer than the prescribed duration would be eliminated without its pharmacological effect, function as a placebo, or result in side effects.

Discoveries led by Dr. Aloke Finn's CV Path laboratory have pioneered the understanding of the underlying pathological and anatomical mechanisms of DESs and DCB. Tanaka et al. [11] recently published a pharmacokinetic comparison between polymeric encapsulated microcarriers (Selution SLR mDCB) and liposomal nanocarriers (MagicTouch nDCB), which proves that polymeric particles have a longer circulation time compared to lipid nanoparticles.

Important

PK values from polymeric microspheres include both encapsulated drug and free drug. The drug may be present and contribute to PK value but may not be truly bioavailable due to the polymeric encapsulated layer. On the other hand, polymeric encapsulated drug **nanoparticles** might have a shorter half-life due to relatively faster in-vivo polymer degradation, making bioavailibility of drug adequately and hence could be more efficacious compared to **microparticles**. The same principle would apply to liposomes due to their faster in-vivo dissolution. Therefore, true PK values are amount of drug which is ready to bind cellular targets (i.e. free drug) but not drug which has longer circulation time as protected through encapsulation layer.

Drug coating on DCB is typically formulated by integrating drug nanocrystals into excipients. Lipophilic drugs remain suitable for DCB coating despite poor solubility profiles. Paclitaxel drug retention in the vascular wall has been higher compared to sirolimus [4]. Hydrophilic excipients are admixed to increase coating physical stability and curtail drug loss during transit through the bloodstream by promoting gradual drug release. Nanoparticles are also taken up more efficiently by cells than microparticles [22]. This is advantageous when drug targets, such as paclitaxel or sirolimus, have intracellular targets [23, 24]. Nanoparticles can also efficiently deliver biological cargoes, such as RNA, DNA, and antisense, inside cells [25, 26]. In addition, nanoparticles protect these biological agents from rapid degradation.

Nanoparticles with cationic surfaces have a notably increased tendency to permeate (and perforate) cellular membranes compared to neutral or anionic nanoparticles; however highly cationic charged nanoparticles are prone to cause cell toxicity [27].

Intrinsically, only a small fraction of the drug coating transfers to the tissue surface during balloon inflation; most of the coating is lost/eliminated within 24–48 h, indicating that dose efficiency can be poor. The performance of DCB depends substantially on the coating composition and microstructure. Experiments evaluating balloon coating interactions with arterial tissue demonstrate that both chemical additives and intrinsic properties, such as particle size and crystallinity, modulate coating morphology, consequently resulting in acute drug transfer. Mechanical testing, biophysical modeling of coating-wall interactions during simulated deployment, and cellular viability studies further elucidate the relative impacts of chemistry and microstructure on coating adherence, drug delivery, and drug efficacy.

8.3 Materials Used as Drug Carriers

A wide variety of materials, such as lipids, polymers, and peptides, is most favorable due to their versatile applications. Such biodegradable and biocompatible materials are expected to play a keystone role in the development of drug delivery devices and implants. Unlike conventional polymeric devices, nanoscale delivery systems enable the targeting of drugs to specific organs, tissues, or intracellular compartments, thereby offering distinct benefits in diagnostic and/or therapeutic applications.

Among the substances employed in nanotechnology, several are biologically inspired and consequently degrade via natural pathways. These materials achieve controlled drug release by tailoring their size and shape, as well as modifying their surfaces with different functional groups, thereby demonstrating a strong correlation with biocompatibility and toxicity. Examples of the principal materials utilized in nanotechnology include biodegradable polymers, nanoparticles, organic–inorganic hybrids, quantum dots, and carbon nanotubes, each exhibiting distinctive properties [28, 29].

Polymeric drug delivery constitutes an integral component of DCB, fundamental to their efficacy and safety. The utilization of polymers on drug-coated balloons is closely linked to current developments in nanotechnology. The drug-eluting stent, with its coating applied to the stent, is a drug-polymer matrix that has higher adhesion strength. In contrast, on DCB, due to their moderate coating integrity, detachment of the coating layer determines the drug delivery. The mechanisms governing the transition from nanocarriers to the release of their payload within biological environments remain incompletely understood. Polymers are frequently combined with additional materials to form composite structures, with evidence suggesting their utility in advanced nanomaterials [30].

8.4 Biocompatibility Testing Strategies for Nanomaterials

The following recommendations reflect the ongoing evolution of international standards from ISO, OECD, ASTM, and regulatory frameworks such as REACH. They underscore the importance of adopting nanoparticle-specific and formulation-specific testing strategies in the assessment of nanomaterials used in medical devices. Further, the FDA does not have a universal definition or a single regulatory pathway for nanomaterials for biocompatibility testing. Instead, each product is assessed individually, considering its intended use, composition, and potential risks. Therefore, the FDA require early discussion during development stage to clarify regulatory expectations.

8.4.1 Overview of Nanomaterial Testing

Testing nanomaterials necessitates a tailored approach owing to their distinctive physicochemical characteristics and interactions with biologi-

cal systems. During sample preparation, nanomaterials extracted in a variety of solvents / media may result in the presence of visible or invisible particulates. The chosen processing method, such as centrifugation, filtration, or ultrafiltration, will be dictated by the nature of these particulates. These particulates can interfere with biocompatibility assays, leading to erroneous results and complicating the interpretation of data.

ISO/TR 10993-22 outlines key parameters for the physical and chemical characterization of nanomaterials in medical devices, referencing ISO/TR 13014 for aspects such as chemical composition, particle size and distribution, aggregation state, shape, surface properties, solubility, and other relevant factors. Biocompatibility testing per ISO 10993-1 often requires both chemical and biological assessments, with special extraction considerations for nanomaterials, such as avoiding sample filtration and accounting for nanostructured surface irregularities. Soluble nanomaterials act similarly to non-nanoscale materials, while insoluble ones remain as dispersed particles, requiring direct hazard assessment. The guidance also emphasizes nanomaterial uptake by mammalian cells, potential assay interferences, and variable kinetics based on particle size.

8.4.2 Cytotoxicity Assessment

For cytotoxicity evaluations, employing multiple cell lines, including both phagocytic and non-phagocytic types, is recommended to effectively capture variability in particle uptake. Additionally, it is important to consider particle number and surface area as dose metrics, rather than relying solely on mass, in order to reflect the exposure scenario more accurately.

8.4.3 Sensitization

Sensitization testing for nanomaterials used in medical devices should account for the protective function of the skin barrier, which significantly influences particle interaction and penetration. While traditional assays, such as the guinea pig maximization test (GPMT) and the local lymph node assay (LLNA), are commonly utilized to assess skin sensitization, they may not be fully appropriate for nanomaterials due to the unique properties and behaviors of these materials. Emerging in-vitro assays, including those designed to evaluate dendritic cell activation, show promise for identifying sensitization risks without the need for animal testing. However, these alternative methods require further validation and standardization before they can replace established techniques.

8.4.4 Irritation

For irritation assessments, intracutaneous reactivity tests are preferred, as they bypass the stratum corneum and more accurately reflect exposure to nano-objects.

8.4.5 Hemocompatibility Testing

Hemocompatibility testing of nanomaterials should include assessment of complement activation, platelet aggregation, and protein adsorption. Free nano-objects, due to their high surface-to-volume ratio, can trigger abnormal immune responses.

In the context of drug-coated balloons (DCB), it is important to evaluate the thrombogenicity of both stand-alone catheters and DCB as finished device.

8.4.6 Systemic Toxicity and Implantation

Systemic toxicity testing should focus on organs that are part of the mononuclear phagocyte system (such as the liver and spleen), as well as the kidneys and brain. Advanced imaging techniques like transmission electron microscopy (TEM) are recommended, since light microscopy may not provide sufficient information for nano-

material detection. For implantation tests involving nanomaterial drug-coated balloons (nDCB), direct injection into tissues may not be clinically relevant; therefore, studies in large animal models, such as porcine models, are advisable which mimics clinical setting.

8.4.7 Genotoxicity

Uncertainty regarding nanoparticle uptake may affect the results of bacterial reverse mutation tests, making careful test selection crucial. The mouse lymphoma assay is a potentially useful alternative since it uses mammalian cells, which may better represent the biological context.

8.4.8 Importance of Tailored Testing Strategies

International guidelines emphasize the necessity for nanomaterial- and formulation-specific testing strategies for medical devices, due to the unique physical, chemical, and biological properties of nanomaterials. Key standards, including ISO/TR 10993-22 and ISO 10993-1, recommend customized sample preparation and biocompatibility testing, with a focus on assay interferences and nanomaterial uptake by cells. Cytotoxicity and sensitization assessments should use multiple cell lines and advanced in-vitro assays, while irritation, hemocompatibility, systemic toxicity, and implantation testing require specialized approaches tailored to nanomaterial properties. Ongoing validation of new testing methods is essential to ensure the accuracy and relevance of safety evaluations for nanomaterial-enabled medical devices.

Therefore, customized selection of tests and careful consideration of evaluation criteria should be applied to prove safety of nano-formulation.

8.5 Manufacturing Complexities

The manufacturing of DCB presents considerable complexity. Integrating a nanotechnology coating that achieves uniform drug loading further amplifies these complexities. Nanotechnology underpins the design of such drug-releasing systems [31], enabling the development of pharmaceuticals and current DCB to progress into the next generation of lesional treatments.

Paclitaxel, in combination with contrast agents such as iopromide, represents a typical microparticle drug–excipient system that simultaneously enhances paclitaxel solubility, delivers antiproliferative effects on vascular smooth muscle cells, and inhibits restenosis, all while avoiding added toxicity. Excipients such as triacetin and acetylated α-cyclodextrin further serve as effective drug carriers [3]. However, a prominent challenge arises from mixing lipophilic drugs with hydrophilic excipients, which can yield unstable, highly crystalline coatings that tend to form particles. These particles pose risks of downstream vascular embolisms when collected at distal capillaries or myocardium [4]. A possible chemistry could be that the drug's insoluble crystals in the blood environment cause flocculation instead of dispersion due to its hydrophobic properties and poor surface tenstion. Careful adjustment of the drug-to-excipient ratio, typically favoring a low drug-to-excipient mass ratio, and the application of the drug coating technique can minimize crystalline formation, reduce microparticle generation, and reduce drug coating thickness [5, 32]. A thin, smooth coating characterized by moderate solubility or dispersibility effectively diminishes drug scouring and the potential for less embolization.

Various coating techniques, including impregnation (dip-coating), microdroplets, inert-air assisted spraying, and ultrasonic spraying, are employed to produce smooth drug coatings. While impregnation methods experience declining uniformity with increased drug solution concentration, air spraying and ultrasonic jet-spraying can achieve high uniformity despite relatively low yield during manufacturing. Consequently, the development of enhanced coating methodologies that prevent flaking while improving uniformity and mitigating embolic complications remains a pertinent objective.

A persistent challenge in nano-enabled drug formulation manufacturing is the handling and

retention of nanoparticles throughout the production and shelf-life process. Shelf life is influenced by chemical quality attributes, such as drug degradation and leakage, and physical factors, like surface coating and particulate matter. Chemical attributes are regulated under ICH guidelines, while physical coating assessment criteria vary by DCB manufacturer, sterilization process and differ in their acceptance level across regulatory agencies within the test methods of ASTM 3320.

Another major hurdle in developing nanoformulations for small-molecule drugs is their inherent instability. Drug nanoparticles tend to agglomerate into larger particles, diminishing their dissolution benefits. This requires two key research priorities: developing scalable manufacturing methods and implementing rapid stabilization techniques to prevent agglomeration and preserve particle integrity during production and storage.

Emerging nano-manufacturing technologies must be assessed for their ability to produce diverse nano-formulations, comply with GMP regulations, and support continuous process upgradation. Additionally, controlling critical quality attributes, especially in bottom-up synthesis, remains difficult at scale. Mastery of these controls is essential for reliable product performance and regulatory approval.

8.6 Regulatory Approach

Extensive research is underway to harness these advantages for next-generation DCB; however, translating such innovations from the laboratory to the clinic remains complex due to inherent regulatory challenges and less regulatory guidance.

Currently, the United States Food and Drug Administration (FDA) does not consider every product containing a nanomaterial to be a nanotechnology product. Although nanomaterials fall within its jurisdiction if they fall under a regulated product area [33, 34], this ultimately leads to misbranding, resulting in Notice of Inspectional Observations. Existing federal laws governing drugs, medical devices, and biological products provide a sound basis for informed decisions regarding nano-related products. However, no product-specific regulations apply to product types outside the scope of existing authorities, creating uncertainties for products that do not fit neatly into current regulatory pathways.

The FDA's regulatory approach to nanopharmaceuticals emphasizes early consultation during product development to address safety, effectiveness, and public health considerations. A scientifically focused premarket review process is applied, along with post-market safety monitoring. Nanotechnologies, such as liposomes and dendrimers, require detailed characterization of their physicochemical properties, stability, and studies on ADME to ensure safety and efficacy [33].

Most nanotechnology-related products are subject to health and safety regulations that can vary by jurisdiction; proposals are under development to harmonize approaches across regions, facilitating regulatory progress and market access [35]. The EU definition of nanomaterial is also mentioned in Regulation (EU) 2017/745 on medical devices which specifies a nanomaterial as a natural, incidental, or manufactured material containing particles where 50% or more of the particles have one or more external dimensions in the range of 1–100 nm, with specific inclusions for certain fullerenes, graphene flakes, and single-wall carbon nanotube. The European Regulatory Framework for medicinal products for human use is based on Directive 2001/83/EC on Medicinal Products for Human Use (EC, 2001), which regulates the European marketing authorization and is supplemented with Directives and Commission regulations.

Despite the availability of approved formulations, liposomal, dendrimer-based, PEGylated, and albumin-bound compounds, regulatory compliance remains a significant hurdle and the same applies to nDCB. Discovering new medicines (Drug Discovery) is inherently expensive, time-consuming, and competitive; the unique features of nanostructures further necessitate meticulous attention to ensure the safety of final products, manage development risks, optimize dosage, and facilitate successful patient stratification.

8.7 Challenges in Research and Development

Designing and fabricating next-generation DCB continues to challenge several groups, encouraging the development of various DCB types. Nations across the Americas, Asia, and Europe regard nanotechnology as a driver of economic growth, high-tech jobs, and sustaining international competitiveness. More than sixty countries have established dedicated campaigns to explore the potential benefits of nanoscale science and technology for energy production, medicine, environmental remediation, and electronics applications.

The complexity of manufacturing, cost, and rigorous testing to ensure bioequivalence, safety, and efficacy against existing treatments present obstacles that have only recently been overcome.

From a characterization perspective, DCB typically feature an excipient, a drug, and a delivery balloon. A variety of each component-cum-material combination exists, some widely employed, with considerable work to ascertain optimal configurations of excipient, drug, and carrier. Yet, the extraction of nanoparticles in the right organic solvent before testing drug quantification is challenging, and the validation of test methods is challenging due to the sensitivity of nanoparticles.

Safety and efficacy testing constitute a fundamental stage in the development of drug delivery systems. In-vitro and in-vivo studies play a crucial role in understanding drug release kinetics, pharmacokinetics, and therapeutic efficacy. Keratose, for example, has undergone synthesis optimization and formulation evaluation for such purposes [36]. Medical devices with nano drug delivery may require specialized techniques for physicochemical characterization and biocompatibility testing, including extractable and leachable testing with additional considerations. Despite the FDA's guidance on ISO10993-1, the FDA recommends manufacturers to submit test methods prior to initiation of any tests (Section VD).

To investigate average particle size diameter, the most common and cost-effective method is dynamic light scattering (DLS). However, DLS measures only the hydrodynamic diameter and assumes spherical particles, making it less accurate for non-spherical shapes or highly polydisperse samples. During the development stage, more advanced techniques such as scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDS), transmission electron microscopy (TEM), atomic force microscopy (AFM), and X-ray photoelectron spectroscopy (XPS) are often employed for detailed characterization.

8.7.1 In-Vitro Dissolution and End-Product Specifications

Establishing end-product specifications is a crucial step in the development of nano-enabled drug delivery systems. Among the various critical quality attributes, in-vitro dissolution (IVD) plays a significant role in determining batch-to-batch variability. Although numerous FDA-approved formulations exist utilizing polymeric, liposomal, and RNA-based vehicles, the process of setting up reliable IVD methods remains challenging. These challenges stem from the variability of biological environments and physiological conditions, which can impact the consistency and reproducibility of dissolution results.

To address these challenges, it is essential to adopt a customized IVD approach. This involves the careful selection and justification of key parameters, including the identification of the appropriate elution medium and assessment of drug compatibility and stability within that medium. The choice of elution medium must be tailored to the specific formulation to ensure accurate measurement of drug release characteristics.

In terms of apparatus, using a dialysis chamber can offer advantages for measuring drug dissolution. However, practical issues such as sample handling and achieving repeatability present significant obstacles. Ensuring consistent

sample processing and reproducible results is critical for the validation of IVD methods, and these aspects require particular attention during method development.

The final method and acceptance criteria should be capable of detecting differences between batches (e.g., variations in formulation or manufacturing process) and rejecting any batches that do not meet predefined quality standards.

8.8 Clinical Utility

The members of the vascular interventional medicine community are the first to benefit from advancements in DCB technology, but widespread application will transform other specialties as well. DCB Academy, led by Prof. Bernardo Cortese, has been a pioneer in spreading clinical benefits of the "leave nothing behind" and "stentless" strategy in PCI where possible. Continued development is anticipated to decrease late lumen loss and improve target lesion vascularization after angioplasty, making it a preferred tool for many arterial diseases. With ongoing research, a variety of specialized DCB tailored to diverse clinical conditions is expected to emerge.

Important
The unanswered question is whether one DCB formulation / drug fits all vascular applications, and the answer is "NO." Drug resistance in coronary and peripheral vascular applications has not yet been investigated [17, 35, 37–41]. Drug resistance can be addressed by both sirolimus- and paclitaxel-based nanoparticle drug delivery. Kwai et al. data support proof of concept on dual-drug delivery and clinical possibility to overcome such challenges [17].

Peripheral arterial disease (PAD) involves atherosclerosis of the noncoronary vessels and manifests as intermittent claudication or more severe forms such as critical limb ischemia with rest pain, ulceration, or gangrene. nDCB catheters, which provide a homogeneous deposition of antiproliferative drugs within arteries, offer a promising strategy to inhibit neointimal proliferation following vascular injury, potentially reducing restenosis without the need for permanent implants [42–45].

mDCB elute paclitaxel to locally inhibit neointimal growth, thereby enhancing patency rates while reducing the incidence of restenosis and the need for repeat revascularization. While clinical data demonstrate that DCB angioplasty is a reliable and safe procedure, its impact on critical outcomes such as limb salvage and mortality remains to be determined. Consequently, further research is warranted to quantify the clinical and functional benefits of DCB therapy and to establish its cost-effectiveness.

8.9 Future Considerations

Nanotechnology offers promising improvements for DCB by enabling the development of advanced drug delivery systems made from biodegradable and biocompatible materials that specifically target diseased areas. Additionally, nanoparticles can be engineered to achieve controlled pharmacokinetic profiles, allowing for triggered release mechanisms. A major technological challenge for next-generation DCB involves surface modification of devices with functional materials that incorporate nanoparticles capable of releasing therapeutic agents through diffusion or dispersion. At the same time, nanotechnology can provide better safety compared to micro- or crystal-based DCB. Therefore, nanotechnology serves as a transformative approach that enables controlled drug delivery across various length scales, with important implications for drug-eluting stents and, in the future, DCB.

8.10 Conclusions

Nano-enabled DCB are a flexible, indication-specific platform, not a one-size-fits-all. Success hinges on controlling nanoscale attributes (size,

shape, crystallinity, and surface chemistry), coating microstructure, and deployment mechanics to couple efficient acute transfer with clinically relevant durability while minimizing particulate risk. Development priorities include standardized particulate/PK frameworks, robust GMP-scalable unit operations, and stability programs that preserve nanoparticle integrity while maintaining robust quality control parameters. Regulators expect transparent, nano-specific methods, comprehensive characterization, and ISO 10993 aligned biocompatibility supported by FDA/EU engagement. Next-generation advances in dual-drug constructs, functionalized surfaces, and triggered release may address resistance and extend benefits. Addressing unmet clinical needs by generating translational models, and endpoints to each vascular bed will accelerate safe adoption in clinical practice.

Competing Interests VL is the inventor of Dual API nanotechnology. The Cleveland Clinic licensed the technology to Advanced NanoTherapies, Inc. Dr. Labhasetwar serves as a consultant and has equity in Advanced NanoTherapies, Inc. His conflict of interest is managed by the Conflict-of-Interest Committee of the Cleveland Clinic.

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9 How to Design an Impactful Animal Study for DCB Assessment?

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9.1 Introduction

Over the past decade, interventional therapy for coronary artery disease (CAD) and peripheral artery disease (PAD) has rapidly advanced, driven by the extensive accumulation of data, enhancements in interventional techniques, and the evolution of devices and drug technologies. Although balloon angioplasty is initially effective in restoring blood flow, restenosis due to vessel recoil and neointimal hyperplasia occurs in more than 50–60% of patients within 1 year post procedure [1, 2]. The development of stent technology has effectively addressed these issues, with the currently available new-generation drug-eluting stents (DES) becoming the preferred treatment. However, clinical studies have indicated an increased risk of late events and neoatherosclerosis in patients who underwent DES implantation [3]. Additionally, leaving behind a metallic scaffold may not be the most appropriate strategy for complex lesions. Permanent stent deployment can lead to in-stent restenosis, which may potentially limit future treatment options. Drug-coated balloons (DCB) have emerged as an alternative to stent implantation for CAD [4]. The primary advantage of this technology is the uniformity and short-term transfer of the drug to the luminal surface without the need for a permanent scaffold and a polymer carrier. The concept of "leaving nothing behind," i.e., no permanent metallic stent scaffold, is attractive in complex lesions such as small vessel disease, bifurcation lesions, and in-stent stenosis [5–7], and studies are ongoing testing DCB against other currently available therapies. The advent of DCB in endovascular therapy (EVT) has facilitated an available alternative to stent implantation for the treatment of femoropopliteal artery disease. DCB treatment for the femoropopliteal artery has become mainstream. Animal experiments have contributed to the development of DCB technologies. In preclinical studies, the primary focus is on evaluating the safety of the device being tested. The specific approach depends on the device in question and its clinical use, but regardless, it is essential to demonstrate that the device is safe for use. While demonstrating efficacy is important in the clinic, this is not practical in healthy animals; in such cases, showing equivalency of vascular responses to the existing device may suffice. Before starting the preclinical testing process, it is crucial to understand the anatomical differences between human and animal models, as these differences can significantly impact the results. The current chapter will

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summarize recent animal studies focused on the evaluation of the efficacy and safety of DCB.

9.2 The Concept of DCB Studies in Animal Experiments

Percutaneous balloon angioplasty for CAD was first performed by Andreas Grüntzig in 1977 [8]. However, treatment was associated with high rates of restenosis after balloon dilatation. The mechanisms responsible for late lumen loss after balloon angioplasty are predominantly the formation of a fibrocellular neointima at the site of dilation and arterial negative remodeling [9, 10]. Mechanical stress induced by balloon angioplasty causes injury to endothelial cells and the medial wall, leading to plaque cracking. This is followed by a repair mechanism involving platelet fibrin deposition, inflammation, the release of growth factors, and smooth muscle cell (SMC) proliferation, accompanied by subsequent deposition of matrix proteins. Stimulation of cell cycle proteins and mitosis culminates in the final common pathway leading to intimal hyperplasia [11]. Pathological findings in patients who died several months after apparently successful coronary angioplasty have demonstrated evidence of previous fracturing of the atheromatous plaque and medial dissection, with extensive neointimal proliferative tissue filling the crevices, overlying the plaque, and obstructing the coronary lumen [12].

DCB are an innovative approach to delivering anti-proliferative drugs directly to the arterial wall without the need for supporting stents. Clinical studies have shown that treatment with paclitaxel-coated balloons (PCB) results in reduced late lumen loss and target-lesion revascularization compared with plain old balloon angioplasty (POBA) [13, 14]. Examining the drug concentration and histological data regarding the response on vessel walls, particularly the endothelial cells and SMCs, is required after DCB in preclinical experiments. Meanwhile, some concerns regarding drug loss into the systemic circulation were raised. Previous data have demonstrated that the introduction of DCB catheters via sheath into the coronary arteries, followed by their retrieval without inflation, resulted in a 6% reduction in the active ingredient [15]. Variable coating integrity has been reported, with paclitaxel-urea and paclitaxel-iopromide DCB experiencing 20–40% paclitaxel loss when inflated and shaken in an empty vial [16]. The loss of paclitaxel into the body, rather than exclusively at the target site, raises the potential for embolization of the drug and excipients. In addition, some clinical case reports have been published on vasculitis after DCB treatment to PAD [17, 18].

Therefore, animal experiments for DCB have been conducted based predominantly on these two critical concepts: (1) efficacy: the focus is on examining the potential therapeutic effects of delivering anti-proliferative drugs using assessment of pharmacokinetics, histomorphometry, and histology of the DCB-treated arterial segment; and (2) safety: it is essential to ensure the absence of evidence of systemic toxicity, distal emboli, or vascular changes, which includes monitoring for signs of vasculitis and other potential side effects that could arise from drug loss during the procedure. These concepts form the foundation of DCB studies in animal models, aiming to optimize both the efficacy and safety of DCB before their application in clinical settings. It is important to note that effectiveness is difficult to demonstrate in healthy animals, and for the most part, surrogate measures such as pharmacokinetic data and evidence of histologic drug effect are used in lieu of angiographic reduction in stenosis (which is rarely seen).

9.3 The Mechanism for Drug Effectiveness

9.3.1 Drugs Used in DCB

The primary drugs used in DCB are paclitaxel and sirolimus, anti-proliferative agents known for their ability to inhibit smooth muscle cell proliferation, which is a major cause of restenosis following angioplasty. Table 9.1 shows the summary of unique DCB materials, including paclitaxel and sirolimus, available for PAD treatment.

Table 9.1 Summary of leading commercially available DCB

DCB	Company	Drug	Drug Dose (μg/mm^2)	Microparticles	Drug Carrier (Excipients)	Indication
IN.PACT™ Admiral™	Medtronic	PTX	3.5	Small	Urea	PAD
Lutonix®	C.R. Bard	PTX	2.0	Larger	Polysorbate/sorbitol	PAD
Stellarex™	Philips, Amsterdam	PTX	2.0	NA	Polyethylene glycol	PAD
Ranger™	Boston Scientific	PTX	2.0	Small	Acetyl tributyl citrate	PAD
Kanshas®	Terumo Corporation	PTX	3.2	Smallest	L Serine ethyl ester HCl	PAD
MagicTouch™	Concept Medical	SRL	1.27	NA	Phospholipid	PAD, CAD
SELUTION SLR™	Cordis	SRL	1.0	NA	Microreservoir and CAT™, amphipathic lipid	PAD, CAD

CAD coronary artery disease, *CAT* cell adherent technology, *DCB* drug-coated balloon, *HCl* hydrocholoride, *NA* not applicable, *PAD* peripheral artery disease, *PTX* paclitaxel, *SRL* sirolimus

Paclitaxel stabilizes microtubules and inhibits cell proliferation at the G2/M phase of the cell cycle [19, 20], which reduces neointimal hyperplasia, a common cause of restenosis. The structure of solid-phase paclitaxel on the balloon surface can range from amorphous to crystalline [21]. Amorphous paclitaxel exhibits durability during tracking and effectively transfers the drug to the vessel wall, but its permanence and bioavailability over time is limited. Meanwhile, the crystalline form tends to have a more prolonged pharmacokinetic and biologic effect due to slower dissolution rates [22]. For an efficacious DCB, it is essential to have an optimal mix of amorphous and crystalline paclitaxel, as well as the appropriate excipient. The dosage of paclitaxel on DCB typically ranges from 2.0 to 3.5 μg/mm^2. Studies have shown that this dosage is effective in maintaining therapeutic levels in the vessel wall for an adequate period, ensuring prolonged anti-proliferative action. The high lipophilicity of paclitaxel allows for passive absorption and retention in the vessel wall, which contributes to its sustained therapeutic effect [23].

Sirolimus has the capacity to reversibly bind to FKBP12, thereby exerting a potent inhibitory effect on cell proliferation. This is accomplished by forming a complex with the mammalian target of rapamycin, resulting in a blockade of cell cycle progression at the G1/S transition [24]. Sirolimus has a wider therapeutic range and greater anti-restenotic and anti-inflammatory effects than paclitaxel, which is one of the major reasons why paclitaxel-eluting stents are no longer used in coronary arteries [25]. The efficiency and safety of sirolimus-coated balloons (SCB) have been shown in several clinical and preclinical studies [26–28]. Because tissue absorption is limited following acute transfer, the success of sirolimus DCB hinges on the effective delivery of anti-proliferative drugs, facilitated by innovative excipients and carriers and the efficacy and safety of the drug itself.

9.3.2 Drug Carriers in DCB

Drug carriers are crucial in DCB technology as they facilitate the transfer and retention of the drug in the vessel wall. They help solubilize the drug, enhance its uptake, and ensure its sustained release. Urea, which is used in products such as IN.PACT™ Admiral™ (Medtronic, MN, USA), is a hydrophilic excipient that enhances the solubility of paclitaxel and improves its penetration into the vessel wall, leading to approximately 7% of the drug being solubilized in 24 h [29]. Polysorbate/sorbitol excipients act as surfactants, improving the distribution and retention of the drug in the vessel wall. They facilitate a faster release of the drug, with 51% of the drug being solubilized in just 1 h, and the remainder solubilizing over 24 h [29] [Lutonix® 035 DCB (C.R. Bard, NJ, USA)]. Acetyl tributyl citrate, used in Ranger™ (Boston Scientific, MA, USA), is a carboxylic acid ester that facilitates the release and transfer of paclitaxel into the arterial wall. Polyethylene glycol (PEG) increases the hydrophilicity of the balloon surface, facilitating better drug transfer and reduced wash-off during delivery. PEG is used in Stellarex™ (Philips, Amsterdam, Netherlands), known for their effective drug delivery and clinical performance.

Sirolimus-coated balloons use microcarriers to facilitate drug dissolution over time. Phospholipids, which are used in MagicTouch™ (Concept Medical Inc. FL, USA), comprises one hydrophilic head and two lipophilic tails. This improves the adhesion property of encapsulated sirolimus. Microreserviors in the SELUTION SLR™ (Cordis, FL, USA) consist of a biodegradable polymer intermixed with sirolimus. Microreservoirs are advanced drug-delivery systems designed for consistent, predictable drug release, sustaining effects for up to 90 days. Cell Adherent Technology (CAT™) enhances drug retention and bioavailability by securely binding microreservoirs to the balloon surface. This allows for a lower drug dose and optimizes the transfer and cellular uptake of sirolimus. Advances in micro- and nanoparticle technologies may enhance drug delivery and reduce embolic risks.

9.4 The Rationale, Experimental Design, and Result

9.4.1 Design of Preclinical Studies for DCB

The selection of animal species should be guided by factors such as the similarity in size between animal and human arteries and, in some cases, location; time-dependent tissue response; and healthy or diseased models. The healthy porcine model is much preferred to other animal models and has been utilized to assess the efficacy and safety of catheter-related devices, including DCB for coronary arteries and peripheral arteries, because its anatomy and local reactivity to the devices are similar to humans. Some studies reported differences in neointimal growth and the presence of restenosis between test and control groups due to using models characterized by high vessel injury, such as the coronary in-stent restenosis model, or significant overstretch in the hypercholesterolemic femoral artery model [15, 30, 31]. We have been performing treatment with DCB and POBA (or stent implantation) on the external femoral arteries or coronary arteries of healthy swine. The rabbit model has also been used for the assessment of the treatment area but they are generally not good for laboratory practice (GLP) studies. The rabbit model is not preferred for safety assessment, especially in the coronary artery and downstream, by most government regulatory bodies. The ovine and canine models are mostly used for structural device experiments due to similarities in the size of the structure to human.

In general, studies involving approval for DCB by governing bodies such as the U.S. Food and Drug Administration involve both safety and pharmacokinetic studies.

Safety studies generally consist of an acute timepoint (3 or 7 days) and several chronic timepoints, consisting of 28 days, 90 days, and at least one or two more timepoints after which drug retention in tissues is no longer detectable. For each timepoint, evaluation includes morphometric and histologic evaluation of the treated tissue (artery) as well as downstream organs (skeletal muscle for peripheral interventions or heart for coronary). The goal is to establish whether the arterial wall returns to a fully healed and quiescent state after drug treatment or if any residual inflammation or other toxicities persist. Sometimes these might also be associated with late intimal formation. Downstream organ evaluation examines the potential effect of any particulates released by the DCB and whether they have any effect on downstream tissues. In addition, nontarget organs such as the liver, kidney, and lung, among others, are harvested to determine whether any signs of systemic toxicity exist or whether there is evidence of particulate debris.

For these safety studies, to understand the differences in the effects according to drug dose, DCB treatment groups consisted of single therapeutic dosing with paclitaxel-coated balloons or 3x therapeutic dosing (which is safety margin dosing) consisting of similar overlapping balloons. For repeat inflations, 3 (or 4) sequential/independent balloons are usually used for where each DCB is aligned, using fiducial point(s) visualized by angiography to achieve a 100% margin of coverage. In comparison, POBA, which has no drug coating, has been used as a control group, although it may not be necessary.

9.4.2 Pharmacokinetic Evaluation in the Treatment Area

In general, neointimal formation occurs within the first 7 days to 3 months in humans after balloon angioplasty or stent implantation [32, 33]. Drug presence is required for this period or even slightly longer. *Ideally, drug levels should then decline to facilitate complete vessel healing*. To demonstrate effective performance in the absence of a metallic scaffold and polymer, DCB must deliver and distribute substantial quantities of anti-proliferative drugs to the vessel wall for an extended duration, maintaining therapeutic drug levels within the vessel wall. The choice of transporter excipients and drug selection are crucial in formulating an effective DCB. Such studies should demonstrate drug levels at acute (hours to days) and chronic timepoints (similar to safety

timepoints). Nontarget organs should also be harvested for drug evaluation to make sure there is no evidence of drug permanence in these tissues. In general, PK studies should extend to at least one or two timepoints when the drug is no longer detectable. In addition, nontarget organs should be evaluated by histology for evidence of any drug effects or toxicity.

9.4.3 Examples of Published Data Using Paclitaxel DCB

We first evaluated the biologic effects of the Lutonix DCB, a low-dose 2 μg/mm^2 paclitaxel-coated balloon with a polysorbate/sorbitol carrier, and the pharmacokinetics of the drug in a swine femoral artery model [34]. Femoral arterial and plasma samples were collected at 1 h and at 1, 7, and 30 days after DCB treatment. Pharmacokinetic analysis of treated arteries showed that the paclitaxel concentration peaked at 1 h (mean ~ 59 ng/mg [69 mmol/L]) and there were therapeutic levels of paclitaxel in the arterial wall at least 30 days post treatment (mean ~ 0.3 ng/mg [0.37 mmol/L]). On the other hand, there was no detectable level of the drug in the plasma following 1 day. Gongora et al. revealed the paclitaxel concentration in arterial tissues after treatment with IN.PACT and Ranger were about 50 ng/mg at 4 h and ~1 to 2 ng/mg at 30 days [35]. Also, we reported that the Kanshas® (paclitaxel 3.2 μg/mm^2) (Terumo Corporation, Tokyo, Japan) DCB has relatively higher arterial wall drug levels compared with the other DCB [36]. Figure 9.1 shows the comparison of paclitaxel concentration in arterial tissue within the four varieties of DCB. The inhibitory concentration (IC50) for inhibition of SMC proliferation was reported to be in the 2.0 nmol/L range in cell culture experiments [37]. These findings indicate that retention of the drug within the arterial walls is adequate to prevent restenosis.

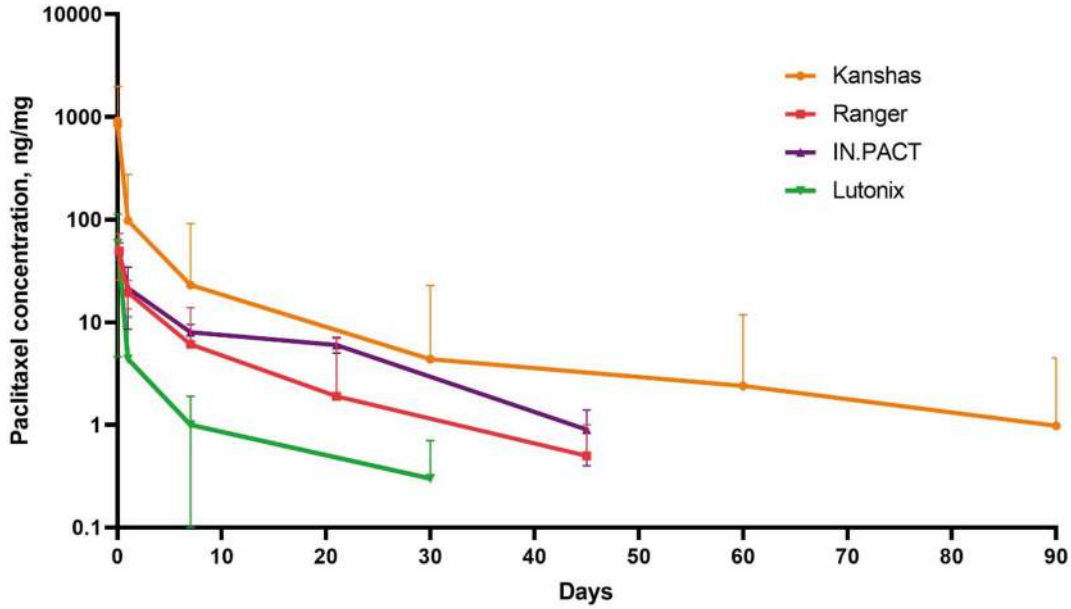


Fig. 9.1 Comparison of paclitaxel concentration in arterial tissue among 4 types of DCB. (The graph was assembled with the data for Kanshas from Sato et al. [36], data for Lutonix from Yazdani et al. [34], and data for Ranger and IN.PACT from Gongora et al. [35]). The concentration decreased immediately after 24 h in all DCB. The values are shown as mean ± standard deviation. DCB = drug-coated balloon. (The citation source is from Sato et al. [36])

9.4.4 The Pathological Findings in the Treatment Area

In the previous study, histology was evaluated at 28 days, 90 days, and 180 days following the procedure with single or overlapping (4×) Lutonix DCB [34]. At 28 days after single and overlapping DCB, there was no evidence of fibrin deposition or loss of endothelium in the intima. Extensive medial or EEL disruption was rarely observed. Inflammation was observed in the DCB group at 28 days, but there was no significant difference between single DCB and the control. Inflammation was absent at 90 days. Medial SMC loss, proteoglycan, and collagen deposition were observed at all timepoints after DCB treatment, and the SMC loss area was maximized at 90 days. The grade of adventitial fibrosis exhibited a progressive increase over time, from 28 to 90 days and continuing to 180 days. These results were significantly higher in 4x overlapping DCB than in single DCB. We separately compared the histological changes between each DCB type using a similar methodology (Fig. 9.2) [23, 38]. The medial SMC transmural loss score with overlapping DCB was significantly greater for IN.PACT Admiral than for Lutonix 035 DCB and the POBA control group at 28 days. We also found that the focal loss of medial SMCs was associated with increased proteoglycan, whereby greater accumulation of proteoglycan was observed in IN.PACT Admiral compared with Lutonix [23]. Between Ranger, IN.PACT, and Stellarex, medial SMC loss in depth and

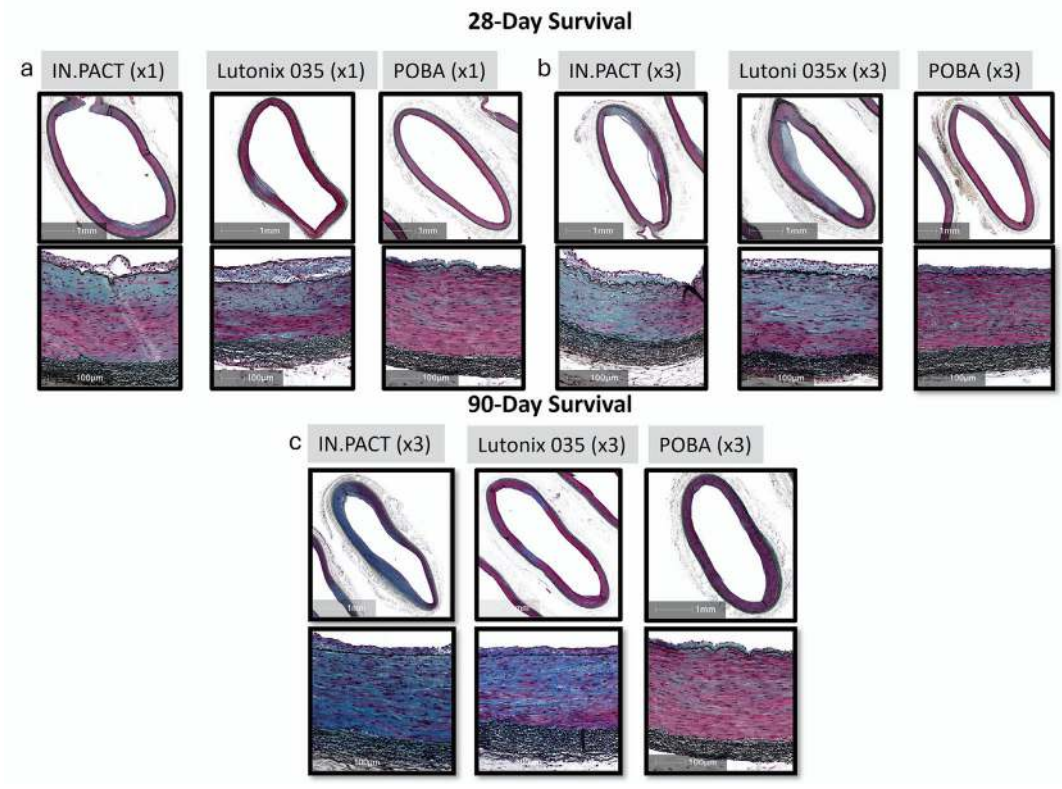


Fig. 9.2 Representative images of the biologic response. Representative images of the biologic response to comparator paclitaxel catheters following dilation of femoral arteries with single (1×, **a**) and overlapping (3×, **b**) balloons at 28 days and overlapping (3×, **c**) balloons at 90 days. Paclitaxel-induced changes are mainly characterized by the loss of medial SMCs with proteoglycan replacement (bluish-green), which is particularly noted for overlapping (3×) balloons. (Modified Movat Pentachrome staining; scale bars: top, 1 mm; bottom, 100 mm) SMC = smooth muscle cell. (The citation source is from Kolodgie et al. [23])

circumference were similar for the 3 DCB treatments [38]. The measured arterial pharmacokinetic levels peaked at 1 h and then rapidly decreased and retained for more than 30 days. Meanwhile, the histopathological changes of the treated arteries with DCB, such as SMC loss, concomitant proteoglycan, and subsequent collagen deposition, peaked at 90 days and were still observed at 180 days. For all DCB, balloon-induced injury of the medial wall was infrequent with rare endothelial cell loss.

9.4.5 Previous Studies Examining the Downstream Organ Impact of DCB

To assess downstream vascular beds after superficial femoral artery treatment, skeletal muscle groups located downstream of the treatment site (gastrocnemius, rectus femoris, semimembranosus, and semitendinosus muscles) and the coronary band are collected and evaluated for ischemic or biological changes, emboli, or signs of systemic toxicity. For the downstream muscles, the arterioles in each histologic section were examined for foreign material, medial arterial wall inflammation, foreign body reactions, emboli, and medial necrosis.

Following Lutonix treatment, changes in skeletal muscle sections were low overall (less than 0.25%) and most of the vascular changes within the skeletal muscle were not evident by 90 and 180 days. The changes were predominantly identified as single or clusters of multiple small vessels with varying degrees of eosinophilic fibrinoid necrosis, SMC apoptosis and loss, and adventitial inflammation or vasculitis, which was primarily composed of lymphocytes. Notably, there was no evidence of ischemia in skeletal muscles after Lutonix treatment at any timepoint [34]. There were more histologic findings of vascular changes after IN.PACT DCB than Lutonix, which was especially notable for IN.PACT DCB (3x). Also, the downstream levels of paclitaxel concentration (ng/g tissue) in the skeletal muscle and coronary band were significantly higher in IN.PACT compared with Lutonix [23]. The percentage of sections with vascular changes was similar in three of the DCB (IN.PACT, Ranger, and Stellarex). Although there were no significant differences in the downstream levels of paclitaxel concentration (ng/g tissue) for the coronary band among three of the DCB (IN.PACT, Ranger, and Stellarex) (911.3 vs 822.5 vs 962.3, $p = 0.5$, respectively), the paclitaxel concentration for the coronary band after IN.PACT was higher (216.5 vs 91.5 vs 101.9, $p = 0.01$, respectively) [38]. Figure 9.3 shows representative images of the vascular changes characterized by fibrinoid necrosis and/or inflammation in the skeletal muscle and coronary band samples downstream from the femoral arteries.

The size of the microparticles coming from the balloon might be associated with the distal emboli. The microvessel size seen downstream was 74 to 85 μm in diameter [34]. In contrast to the downstream assessment, the number of microparticles >200 μm observed was greatest in Lutonix among other DCB in our in vitro experiment [36]. Photographs and SEM images of the microparticles on the surface of the commercially available DCB are shown in Fig. 9.4. The dissolution rate from Lutonix is fast because it consists of polysorbate as a surfactant and sorbitol as a sugar alcohol [29]. Therefore, despite the relatively large size of the microparticles, the downstream effects may be low. It may be insufficient to evaluate the risk of distal embolization based solely on the particle size of the DCB drug.

9.5 The Latest Knowledge and Future Challenges

DCB have become a first-choice treatment for femoropopliteal artery disease, demonstrating excellent clinical outcomes. Clinically, the primary patency rate after DES implantation at 1 year was 82–87% [39] and the Kaplan–Meier primary patency estimates the following 5 years were approximately 69% [40]. Meanwhile, DCB treatment demonstrated a higher primary patency rate at 12 months, accounting for 65–83%, compared with angioplasty with a conventional balloon (55–65%) [41–44]. After DCB treatment at

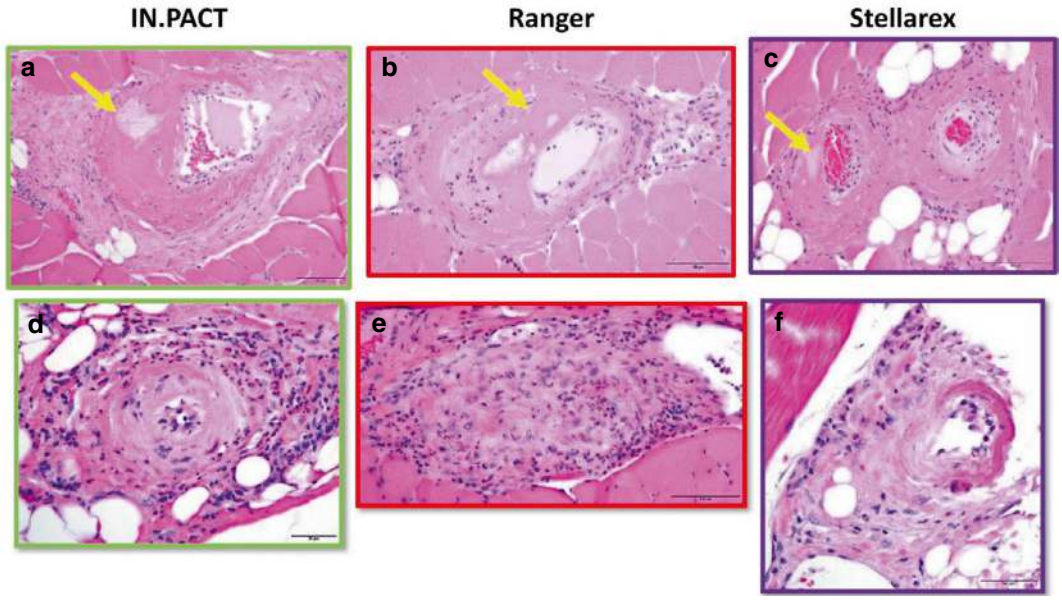


Fig. 9.3 Representative images of downstream nontarget skeletal muscle and coronary band tissues. Representative images of downstream nontarget skeletal muscle and coronary band tissues from healthy swine after treatment of femoral arteries with IN.PACT, Ranger, and Stellarex DCB. Hematoxylin and Eosin-stained sections showing embolic crystalline material (arrows in **a**–**c**) embedded in fibrin and fibrinoid necrosis of arterioles with chronic inflammation and further evidence of nuclear changes, including swelling, pyknosis, and karyorrhexis (**d**–**f**). (The citation source is from Torii et al. [38])

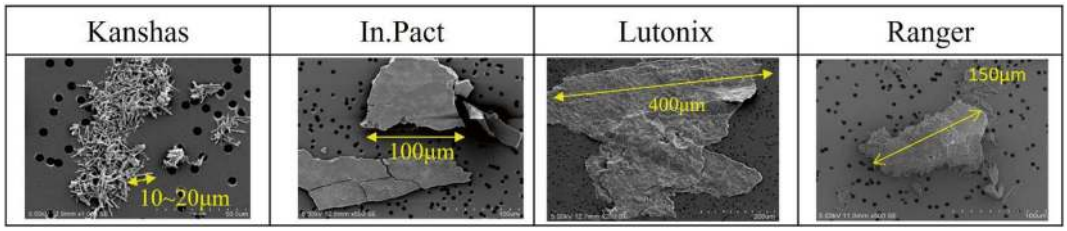


Fig. 9.4 Representative images of microparticles of various types of DCB. The Kanshas DCB showed smaller particles compared with the other DCB. DCB = drug-coated balloon. (The citation source is from Sato et al. [36])

5 years, freedom from clinically driven target lesion revascularization kept a high prevalence of 74.5% [45]. Although there were concerns regarding long-term safety, particularly related to potential downstream embolic effects and mortality rates [46], the U.S. Food and Drug Administration reviewed additional analyses of the risk for late mortality [47–51] and concluded that the data does not support an excess mortality risk for paclitaxel-coated devices in 2023. Nevertheless, further development of DCB technology is required to enhance the long-term patency rate. Additionally, the evidence for PCB in the treatment of below-the-knee (BK) disease is still inconclusive, with several studies yielding conflicting results [52–54]. Nowadays, clinical data regarding SCB has been published and has attracted the attention of cardiologists. Some randomized, controlled trials in the coronary artery field have shown similar efficacy in preventing target lesion revascularization between PCB and PCB [55, 56]. Furthermore, SCB treatment for PAD, including BK lesions, showed promising clinical results sustained at 3 years follow-up in

the XTOSI (Xtreme Touch Sirolimus-coated PTA Balloon for Infrainguinal Arterial Disease) trial [28]. A novel porcine study for SCB treatment effectively reduced neointimal proliferation [57], but there is still a lack of data on the biological effects of PCB and PCB. We are working on the vascular and downstream evaluation after PCB and PCB in porcine coronary arteries. Kawai et al. recently reported the efficacy and safety of a dual active pharmaceutical ingredient (API) DCB, which includes sirolimus and paclitaxel. While each drug possesses distinctive advantages and limitations when administered to the arterial wall, we investigated the potential of combining paclitaxel and sirolimus into a single device to achieve enhanced efficacy and improved safety, using a lower dose of paclitaxel than those typically loaded onto conventional PCB. This study revealed that the dual API DCB exhibited comparable inhibition of cell proliferation to the PCB, albeit at a markedly reduced total drug dose (over 13 times lower than that of sirolimus nanoparticles). The results of animal experiments demonstrated that the dual API DCB is more effective in inhibiting intimal cell proliferation with insignificant downstream embolic effects and myocardial damage compared with the PCB. These findings indicate that dual API DCB have the potential to demonstrate improved clinical outcomes and a greater safety profile than PCB.

9.6 Conclusion

The research and development of DCB have significantly advanced the field of vascular interventions, particularly in the treatment of PAD and CAD. This chapter highlights the importance of well-designed animal studies in assessing the safety and efficacy of DCB. In preclinical studies, accurate selection of animal models is crucial for evaluating the pharmacokinetics, biological effects, and downstream implications of DCB treatment. Pharmacokinetic evaluations have demonstrated that DCB can maintain therapeutic drug levels within the arterial wall for extended periods, which is essential for preventing restenosis. Histopathological analysis further revealed that DCB treatment leads to changes in the arterial wall, including SMC loss and adventitial fibrosis, which are indicative of the drug's effectiveness and long-term impact. These studies also emphasize the importance of understanding the downstream effects of DCB treatment. As the field continues to evolve, future challenges include improving the long-term patency rates of DCB, particularly in BK lesions, and exploring alternative drugs like sirolimus, which may offer better safety profiles and efficacy. The development of dual API DCB also presents a promising avenue for enhancing treatment outcomes and reducing the risks associated with higher drug doses.

In conclusion, the design and execution of animal studies play a pivotal role in the ongoing development and optimization of DCB. These studies provide invaluable insights into the pharmacokinetics, biological effects, and safety of DCB, ultimately guiding their clinical application and improving patient outcomes in vascular interventions.

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Technology; Spectranetics; Surmodics; Terumo Corporation; W. L. Gore; Xeltis.

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10 The Importance of Coronary Lesion Preparation Before DCB Angioplasty

Jasim Hasan, Sara Malakouti, Jacinthe Khater, Irfan Ullah, Krupal Reddy, and Bernardo Cortese

10.1 Introduction

Stent-free percutaneous coronary intervention (PCI) utilizing drug-coated balloons (DCB) is emerging as an innovative approach in coronary artery disease (CAD) management. Unlike drug-eluting stents (DES), which involve metal and polymer components that can trigger inflammatory responses in blood vessels, DCB-based PCI is an alternative. DCB is particularly effective in treating various coronary conditions, including in-stent restenosis (ISR) and de novo CAD [1, 2]. However, proper lesion preparation is crucial for the success of DCB treatment, as emphasized by the DCB ARC Consensus Group. This group of experts defines that an optimal angiographic result requires no flow-limiting dissections, residual stenosis of less than 30% (or a 40% focal one in some lesion settings like long lesions) by visual assessment, and a fractional flow reserve (FFR) value above 0.80. Previous research has shown that when lesion preparation aligns with these DCB ARC recommendations, clinical outcomes improve compared to cases where preparation is inadequate [3].

In line with the "leave-nothing-behind" approach, vessel preparation is essential for effective local drug delivery and vessel compliance. Vessel preparation involves techniques such as undersized balloon pre-dilatation, angioplasty with scoring (ScB) or cutting balloons (CB), or atherectomy. ScB or CB are particularly useful in calcified or fibrotic lesions due to their ability to create controlled plaque incision or dissection with minimal barotrauma, thus reducing plaque shift in bifurcation and ostial lesions [3, 4].

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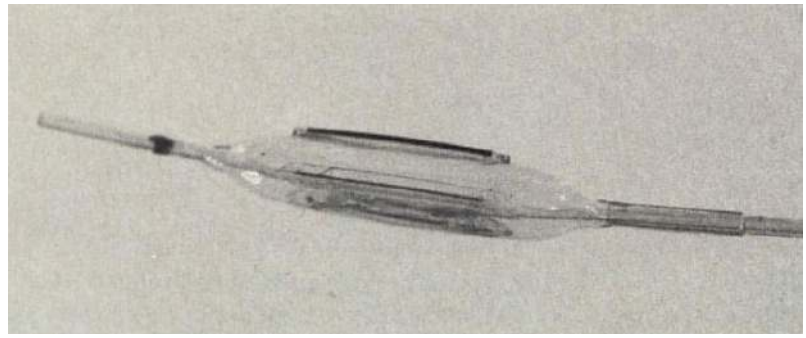


Fig. 10.1 Cutting balloon, first version, by Dr Barath. (This figure is reproduced from Barath et al. [11], with permission)

In severely calcified arteries, the effectiveness of DCB is often reduced due to the mechanical resistance posed by the calcified arterial wall. In such cases, advanced lesion preparation techniques, such as atherectomy or the use of ScB or CB angioplasty, can enhance procedural success and long-term patient outcomes [5–7].

10.2 Historical Perspective of Lesion Preparation

From an historical point of view, the criteria of proper lesion preparation to yield favorable long-term outcomes were derived from the era before stents were the standard of care for CAD. Later, the satisfactory results were first attributed to immediate lumen gain by the stents as compared to balloon angioplasty [8]. This led to the development of the 'stent-like' result defined as a residual stenosis <30% and absence of dissection [9, 10]. With different complex lesions, different devices were developed, all with the goal of proper lumen gain. Dr Barath, by inventing the CB, intended to develop a balloon that can achieve a controlled injury without barotrauma to the vessel, since standard balloons tend to create irregular intimal tears along with stretching and splitting the vessel wall in uncontrolled fashion, which led to a high proliferative response. The CB would achieve (according to Dr Barath's hypothesis) more controlled incisions in the vessel wall without leading to limitations to the flow [11]. One of the earliest DCB trials, PICCOLETO, also failed to demonstrate non-inferiority to stents due to inadequate lesion preparation, performed in only 25% of the DCB arm as compared to 86.2% in the DES arm. This highlights the importance of standard lesion preparation before DCB angioplasty [12, 13] (Fig. 10.1).

10.3 DCB ARC and Lesion Preparation: Developing a Common Language

The drug-coated balloon academic research consortium (DCB ARC) set the ground for a common language among researchers for more standardized approaches, allowing the execution of harmonized studies [14, 15]. In relation to conducting research studies, randomization of patients with respect to lesion preparation categorizes the studies into: studies testing the strategy (randomization before lesion preparation) and studies testing the DCB effect (randomization after lesion preparation). Optimal lesion preparation has been in-depth discussed through the group, which has decided to adopt the old angiographic classification of dissections by NHLBI for the assessment after lesion preparation, whereas intravascular imaging, followed by an evaluation of the depth of dissection (intimal, medial, and adventitial) and the morphology of the dissection (cross-sectional, longitudinal) is left to some selected cases. Moreover, a computational measuring of the dissection area and length was identified as dissection volume. The geographic miss was highlighted and emphasized, whereas adding more length to the chosen DCB as compared to the prepared segment was recommended.

10.3.1 How to Obtain an Optimal Lesion Preparation

Lesion preparation includes various techniques used to achieve adequate plaque modification and vessel expansion, thereby optimizing procedural outcomes, particularly when DCB therapy is intended. Here follows the common methodologies to achieve this goal.

1. Semi-compliant and non-compliant balloons

By applying its force upon inflation, a tension on the vessel wall is produced by balloon inflation, and this will distribute uniformly in the balloon, resulting in a crushing effect on the plaque. Assuming the plaque is soft and non-resistant, the balloon inflation will disturb and redistribute the plaque, leading to the lumen gain required. Different techniques were developed to achieve plaque modification and acute lumen gain at the desired extent.

We commonly recommend *prolonged inflations* and *repeat inflations* [16]; like studies in the early era of interventional cardiology have shown, a second or third inflation can lead to a higher diameter as compared to a single one. Specifically, fibrocalcific, calcific, and restenotic lesions are keen to recoil, and it results more difficult to achieve a controlled and optimal dissection in such cases. Lesion preparation with normal balloons still remains the standard of care in various scenarios, with the limitations mentioned earlier.

Since today, the majority of DCB trials have used semi-compliant (SC) or non-compliant (NC) balloons in the vast majority of the patients, mainly because of: (1) a higher confidence by the operator; (2) the lack of dedicated and deliverable devices untill few years ago, and (3) to lack of evidence, especially for the older trials which invariably excluded complex lesions setting and large coronary vessels. This attitude has recently changed. One of the latest trials, REC-CAGEFREE I, used a lower number of conventional balloons as compared to scoring/cutting, as it was recommended by the trial protocol though not obligatory [17]. In the ISR trials, the earlier trials also recommended an NC balloon to be used and inflated at high pressure if needed [18]. Later studies proved the ScB was better as compared to the conventional balloons [19].

2. Scoring and cutting balloons

In the POBA era, the high rate of restenosis (30–60%) was attributed to either significant residual stenosis, non-satisfactory end of procedure TIMI flow, high-grade dissection, acute recoil, or proliferative vessel response [20]. To tackle this, when DCB were approved, we deemed it important to potentiate our ability to improve the quality of lesion preparation, also by creating controlled dissections. It is thought that such a controlled dissection or incision will carry an ancillary effect of the scoring/cutting balloons that would lead to harmonizing the antiproliferative drug distribution. Another useful technical property of such an approach to plaque modification is the ability to mitigate the watermelon seeding effect and perform better in calcific lesions.

Several studies have evaluated the role of scoring or cutting balloons for lesion preparation before DCB in coronary interventions [5, 19, 21–24]. Overall, current evidence suggests that scoring or cutting balloons are safe and feasible tools for lesion preparation before DCB, with potential procedural advantages, while long-term clinical benefits appear lesion- and context-dependent (Table 10.1).

Applications of Specialty Balloons for ISR Before DCB Use

In the ISAR-DESIRE 4 trial [19], pre-dilatation with a ScB before DCB therapy reduced in-segment diameter stenosis (35.0% vs. 40.4%, $p = 0.047$) and binary restenosis (18.5% vs. 32.0%, $p = 0.026$) at 6–8 months. These findings suggest that ScB improves neointimal modification and drug delivery, enhancing the antirestenotic effectiveness of DCB treatment. A strategy-driven prospective study has shown that the use of ScB prior to DCB leads to advantageous outcomes on hard endpoints. Yet, this study showed an increased number of bailout stenting

Table 10.1 Studies showing advanced lesion modification techniques (scoring or cutting balloon, atherectomy and IVL) before DCB use

Study name/ Author	Country & study design	Comparison	Population and lesion	DCB sample & Follow up	Main findings
Vicente et al. 2022 [21]	Spain Retrospective cohort registry	CB before DCB vs standard DCB	ISR	91 patients 5 years	CB plus DCB showed no significant difference compared to DCB only in terms of TLR (3.9% vs 7.1%, $P = 0.68$)
SCRAP study (Meunier et al. 2023) [22]	France Prospective single center	ScB plus DCB vs DES vs Bailout stent	Stable patients with coronary artery	530 patients 12 months	MACE was 4.0% in DCB group versus DES and bailout stent, which were 13.8% and 9.6%, respectively.
SPARTAN Norwich STEMI Registry (Merinopoulos et al. 2025) [23] NCT04482972	United Kingdom Single center, propensity score matching	ScB plus DCB versus DCB only	De novo CAD patients presented with STEMI	452 patients 3 years	ScB plus DCB showed comparable results in terms of primary endpoint, a composite of cardiac death or unplanned TLR (9.1% vs 6.9%, $p = 0.45$) compared to only DCB
Shin et al. 2023 [5] NCT04619277	South Korea Two centers Retrospective	ScB versus non-scoring balloon before DCB	Coronary artery disease	259 patients 1 year	ScB were associated with decreased risk of severe dissection (9.8% vs. 31.8%, $p = 0.001$) and optimal angiographic outcome (60.7% vs. 28.6%, $p < 0.001$) compared to no scoring balloon, whereas higher residual diameter stenosis (≤30%) in ScB group (68.9% vs. 39.6%, $p < 0.001$).
Fawzy et al. 2021 [24]	UK Retrospective	ScB versus non-scoring balloon before DCB	De novo coronary artery disease	348 patients Median follow-up of 660 days	No significant difference between the two group observed. TLR (6% vs. 8.4%, $p = 0.8$), and MACE (8% vs. 11%, $p = 0.7$).
ISAR-DESIRE 4 (Kufner et al. 2017) NCT01632371 [19]	Germany Multicenter open-label randomized controlled trial	ScB versus standard lesion preparation therapy before DCB	DES-ISR	203 patients 6–8 months angiographic 1 year clinical	There were comparable results in terms of TLR (16.2% vs. 21.8%; $p = 0.26$), LLL, and MI (4.0% vs. 3.4%; $p = 0.73$) between two groups.
Rissanen et al. 2017 [25]	Finland Retrospective single-center study	RA before DCB	Complex calcified coronary Lesions	65 patients Median follow-up 17 months	MACE and TLR at 24 months were 20% and 3%.
Li et al. 2025 [26]	China Retrospective observational analysis	RA plus DCB versus RA plus DES	Severely calcified lesions	124 patients 1 year	The TLR in RA plus DCB compared to RA plus DES was 12.9% vs 6.5%, $p = 0.086$. Whereas in terms of MACE no difference was observed (17.7% vs 12.9%, $p = 0.290$).

(continued)

Table 10.1 (continued)

Study name/ Author	Country & study design	Comparison	Population and lesion	DCB sample & Follow up	Main findings
Dong et al. 2023 [27]	China Retrospective study	RA plus DCB versus RA plus DES	Severe coronary artery calcification	57 patients 12–30 months	TLR in DCB plus RA was 13.79% compared to 18.77% ($p > 0.05$), and MACCE was 7.02% vs 12.28% ($p > 0.05$).
Allan et al. 2019 [28]	Australia Retrospective	RA plus DCB	ISR	26 patients Mean follow-up 19 months	TLR and TVR were observed in six and eight patients.
Shiraishi et al. 2020 [29]	Japan Retrospective	RA plus DCB	De novo lesions	30 patients Mean follow-up period of 13.1 months	At follow-up, all-cause deaths and TLR were observed in six and two patients, respectively
Nagai et al. 2019 [30]	Japan Retrospective	RA before DCB	Calcified coronary lesion	190 patients Mean follow-up 196 days	TLR and TVR were 16.4% and 20.7% at follow-up
Yui et al. 2026 [31]	Japan Retrospective, single-center observational	RA plus DCB versus RA plus DES	Heavily calcified coronary lesions	102 patients 1 year	TVF was higher non-significantly in DCB group compared to DES (15.1% vs 9.9%, $p = 0.14$), whereas TLR was higher in DCB compared to DES (10.2% vs 3.0%, $p = 0.001$)
Takamura et al. 2025 [32]	Japan Retrospective observational study	RA/OA followed by DCB versus DES	De novo calcified coronary artery lesions	94 patients/3 years	Between two groups, DCB vs DES, no difference was observed in terms of TLR (16.2% vs. 13.4%, $p = 0.0843$) and MACE (18.3% vs. 16.2%, $p = 0.13$) at 3 years follow-up.
Mitsui et al. 2023 [33]	Japan Single-center and retrospective	OA plus DCB versus OA plus DES	Calcified de novo coronary lesions	43 patients/1 year	MACE-free rate was 90.3% in DCB compared to 96.6% in DES, $p = 0.136$.
Murai et al. 2025 [34]	Japan Single-center retrospective	DCA + DCB group versus DCA + DES group	Left main (LM) bifurcation lesion	58 patients 5 years	At follow-up, the DCA + DCB had higher TLR compared to DCA + DES (16.4% vs 2.3%, $P = 0.027$), and a smaller luminal gain.
Kobayashi et al. 2021 [35]	Japan Retrospective observational	DCA plus DCB	Left main bifurcation lesion	38 patients 1 year	MACE and TVF were in 10.5% and 10.5% of cases.
Kitani et al. 2020 [36]	Japan Multicenter registry retrospectively	DCA plus DCB	Coronary bifurcation lesions	129 patients 1 year	TVF and TLR were in 10.9% and 3.1% cases.
BENELUX-IVL registry (Oliveri et al. 2025) [37] NCT06577038	Multicenter (Netherlands, Greece, Belgium) Registry	IVL plus DCB versus IVL plus DES	Balloon-crossable calcified coronary lesions	45 patients 12 months	DCB plus IVL showed comparable results in terms of MACE (11.1% vs 7.5%, $p = 0.38$) & TVR (8.9% vs 4.5%, $p = 0.26$) compared to patients treated with IVL plus DES.

(continued)

Table 10.1 (continued)

Study name/ Author	Country & study design	Comparison	Population and lesion	DCB sample & Follow up	Main findings
Kleber et al. 2026 [38]	Germany Prospective observational single arm	IVL plus DCB	Severely calcified coronary lesion	66 patients 4 months angiographic	IVL greatly improves the deliverability of DCB in calcified coronary lesions. The mean late lumen gain was 0.04 mm (95% CI −0.15 to 0.07).
Misawa et al. 2025 [39]	Japan Retrospective, single-center study	IVL plus DCB	Severely calcified de novo coronary lesions	45 patients Median follow-up period of 392 days	DCB following IVL strategy was feasible for severely calcified de novo coronary lesions. TLF occurred in 8.9%.
Picard et al. 2026 [40]	France Multicenter retrospective study single arm	IVL plus DCB	Calcified de novo lesions	14 patients 6 months	At follow-up, TLR was 14.3%.
Sato et al.2020 [41]	Japan Prospective study	ELCA plus DCB versus DCB only	ISR lesions	40 patients 12 months	At follow-up, the occurrence of binary restenosis in ELCA plus DCB were same compared to DCB only (20.0% vs 20.0%) whereas TLR were lower in ELCA plus DCB (10.0% vs 20.0%).
He et al. 2024 [42]	China Retrospective Multicenter	ELCA plus DCB group versus DCB-only group	ISR	75 patients 1 year	The reduction in TLR was more frequently observed in patients from the ELCA + DCB group compared to the DCB group (HR 0.33, $p = 0.048$).
ELDISR Study (He et al. 2025) [43]	China Prospective, single-center, randomized controlled trial	ELCA plus DCB versus DCB only	ISR	110 patients 1 year	TLR was 9.1% in the ELCA plus DCB group versus 23.6% DCB-only group, $p = 0.038$.
Laser-DCB trial (Tonomura et al. 2022) [44]	Japan Prospective, single-center, single-arm study.	ELCA plus DCB	STEMI	62 patients 2 years	Minimal lumen diameters were 3.4 ± 0.5, 3.4 ± 0.6, and 3.4 ± 0.5 mm after the procedure, at 8 months and at 2 years, respectively. Binary restenosis was observed in five patients (8.1%).

(continued)

Table 10.1 (continued)

Study name/ Author	Country & study design	Comparison	Population and lesion	DCB sample & Follow up	Main findings
Harima et al. 2018 [45]	Japan Non-randomized controlled trial	DCB with ELCA group versus Stent with ELCA group versus Stent without ELCA group	ACS	60 patients 6–12 months	MACE rate did not differ across the groups(10%, 4.3%, and 3.5%; $P = 0.22$) while an incidence of TVR was more common (15%, 0,and 4.7%; $P = 0.02$) and the diameter stenosis at 6-months of follow up was greater(25.7 ± 18.2, 14.9 ± 13.1 and 16.2 ± 15.4%; $P = 0.002$) in the DCB with ELCA group.
The DERIST study (Ambrosini et al. 2017) [46]	Italy Multi-centric case-control study	ELCA plus DCB	Coronary artery restenosis In-Stent	80 patients 6 months	The ELCA plus DCB may be an alternative treatment for in-stent restenosis (ISR), TLR in 2% of patients.
Shibui et al. 2021 [47]	Japan Retrospective observational	ELCA plus DCB versus conventional balloon plus DCB	De novo CAD	118 patients 1 year	MACCE was 22.2% in the ELCA group and 17.6% in the conventional group

Legend: *CAD* coronary artery disease, *ISR* in-stent restenosis, *STEMI* ST elevation myocardial infarction, *TLR* target lesion revascularization, *TVR* target vessel revascularization, *CB* cutting balloon, *ScB* scoring balloon, *RA* rotational atherectomy, *DCA* directional coronary atherectomy, *OA* orbital atherectomy, *IVL* intravascular lithotripsy, *ELCA* excimer laser coronary angioplasty, *MACCE* major adverse cardiac and cerebrovascular events, *MACE* major adverse cardiovascular events

following ScB pre-dilatation either because of high-grade dissection or residual stenosis. In patients with adequate lesion preparation following ScB, DCB may have a favorable outcome (MACE 4%). It is worth noting that unstable or high-risk patients were addressed with DES rather than DCB [19].

In a retrospective cohort of 106 ISR cases, CB use prior to DCB did not significantly affect procedural success (100% in both groups) or 6-month TLR rates (4.1% vs. 9.1%; $p = 0.147$), compared with NCB before DCB. Despite higher TLR in the NC balloon group, no significant difference was observed, supporting CB preparation as a feasible strategy for improving procedural success and reducing 6-month restenosis risk, although this result is limited due to small sample and short follow-up [48].

Applications of Specialty Balloons for De Novo or Mixed Lesions Before DCB Use

Unlike the previous study, several other studies showed promising results with ScB. The PASSWORD, a prospective observational, all-comer study [49], evaluated the systematic use of a ScB prior to DCB angioplasty in patients with de novo and ISR lesions (BMS-ISR and DES-ISR). A total of 481 patients (496 lesions) were enrolled, including 377 de novo lesions (78.4%), 19 BMS-ISR (4.0%), and 85 DES-ISR (17.6%). The primary endpoint was target lesion failure (TLF) at 9 months. The study found an overall TLF rate of 3.0% (14/463), with higher rates in the BMS-ISR (5.3%, 1/19) and DES-ISR (6.0%, 5/84) groups. In de novo lesions, the TLF rate was 1.1% (4/360), with no significant differences between calcified and non-calcified lesions

(p = 0.158) or small vs. large reference vessel diameters (p = 0.901). The study concluded that using a non-slip ScB for lesion preparation before DCB angioplasty leads to high procedural success and low TLF rates, especially in de novo lesions.

A study identified modifiable predictors for recurrent TLF after DCB, including residual diameter stenosis (DS), the DCB-to-stent size ratio, and DCB inflation time. The overall TLF rate was 20.3%. Higher TLF was observed with residual DS ≥20%, a DCB-to-stent ratio ≤0.91, and inflation time ≤60 s (Fig. 10.2). When treated with optimal procedural parameters, TLF reduced to 8.3% compared with 66.7% in the non-optimized group ($p < 0.001$). These findings indicate that adequate lesion preparation, sufficient dilation, and prolonged balloon inflation, by improving drug delivery [50].

In a large cohort of patients treated with DCB for de novo coronary lesions, plaque area emerged as a key determinant of outcome. Out of 247 patients who underwent DCB-only, a plaque area ≥58.5% (AUC 0.81) was associated with a higher risk of TLF and was identified as an independent predictor of TLF (hazard ratio 7.59, $P < 0.01$). These findings suggest that achieving a plaque area <58.5% before DCB use is crucial for improving outcomes in stent-less PCI [51].

Conversely, the PREPARE study [52] comparing SC, NC, and ScB, prior to DCB treatment for de novo lesions, showed no differences in hard clinical endpoints (cardiac death, TV-MI, or MACE), but TLR was significantly higher in the ScB group compared to the SC and NC groups (11% vs. 3.4% and 4.7%, p = 0.02). The study results suggest that routine use of ScB for lesion preparation prior to DCB in de novo lesions is not recommended, but probably and ad hoc use in selected lesion types should be pursued.

CB offers enhanced outcomes in terms of lumen gain, restenosis, and revascularization rates compared to traditional balloon angioplasty, especially in calcified or complex lesions. This was proven historically by IVUS, in which the CB showed better lumen gain in calcific lesions and better plaque burden while it achieved similar lumen dimensions in non-calcific lesions [53].

A recent study assessed optimal lesion preparation in 78 patients, with 65% of cases involving moderate to severe calcifications, predominantly involving left main or ostial arteries. In addition to standard balloon pre-dilatation, advanced plaque modification techniques, such as ScB, RA

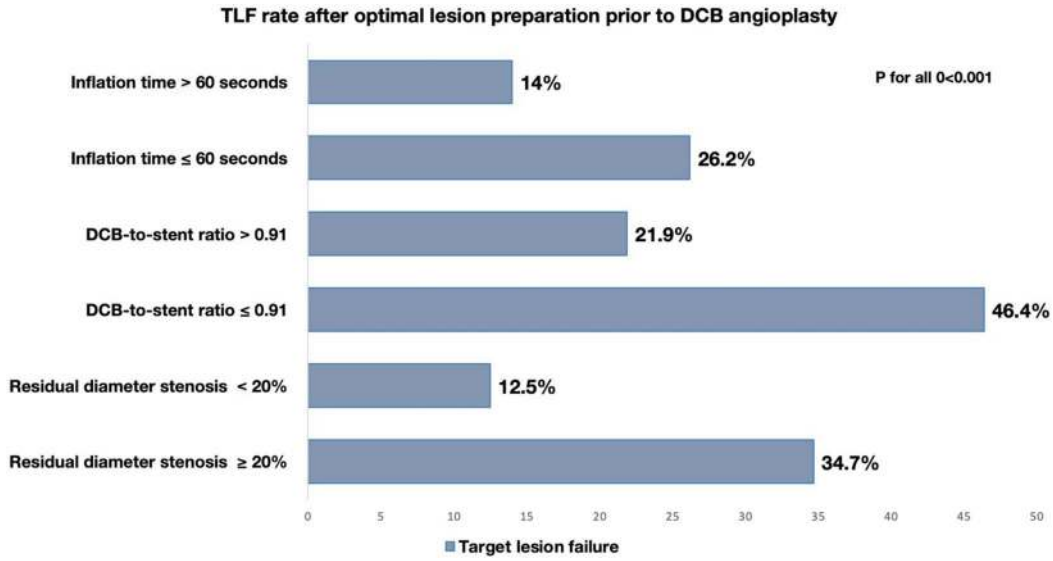


Fig. 10.2 Clinical outcomes after optimal lesion preparation pre-DCB [50]. DCB = Drug-coated balloon; TLF = Target lesion failure

(3.8%), and coronary intravascular lithotripsy (IVL) (15.3%), were utilized. TLR occurred in six patients at 12-month follow-up. Angiographic and procedural success rates were high (98.7% and 97.4%), supporting role of ScB and adjunctive debulking techniques can improve procedural outcomes in complex, calcified lesions [54].

As regards special populations, Merinopoulos et al. [23] explored the use of ScB in the setting of de novo STEMI in a hypothesis-generating retrospective analysis from SPARTAN Norwich STEMI Registry in which 452 patients who benefited from DCB angioplasty were included. One hundred twenty-one patients were treated with ScB and 331 without, without a significant advantage in any study arm.

The ongoing investigator-driven, multicenter PICCOLETO XI study (NCT07391033) is investigating the role of ScB and CB for lesion preparation in a broad population of ISR (Cohort A) and de novo (Cohort B) lesions. Its results are awaited by year 2027.

In summary, ScB and CB are effective for preparing lesions in coronary interventions, enhancing outcomes in both stent implantation and DCB procedures, particularly by reducing dissection and achieving optimal angiographic results. The role of these therapies in selected lesion populations is currently being addressed in dedicated clinical trials.

3. Atherectomy techniques (rotational, orbital, directional, laser)

Rotational Atherectomy

Rotational atherectomy (RA), or rotablation, was introduced over 30 years ago to treat heavily calcified coronary artery disease. Despite a high prevalence of calcified lesions, RA remains underutilized, largely due to lack of standardized protocols, insufficient training, and concerns about procedural complexity and complications.

The procedure typically involves a 6 Fr guiding catheter, accommodating burrs up to 1.75 mm; larger burrs (>1.75 mm) require a 7 or 8 Fr catheter. The most commonly used guidewires are the ROTAWIRE Floppy and Extra Support, or the newer ROTAWIRE Drive, which can be advanced directly into lesions, reducing the need for wire exchanges. Burr sizes range from 1.25 to 2.5 mm, with a burr-to-artery ratio of 0.6 recommended. The smaller burrs (1.25–1.5 mm) are used for tortuous or long lesions, while larger sizes are reserved for aorto-ostial or large vessels. The procedure involves a "pecking" motion of the burr, typically at speeds between 160,000 and 180,000 rpm, with durations of less than 30 s per run. Speeds below 135,000 rpm may lead to burr lodging, while speeds above 180,000 rpm can cause platelet activation and thrombus formation. RA is performed with a flushing cocktail (heparinized saline, verapamil, nitrate, or ROTAGLIDE) to cool the rotablator and flush debris. This technique works by ablation of calcified plaque with a diamond-encrusted burr, rotating at high speeds to modify plaque and facilitate subsequent balloon dilation and stent implantation [55].

Rotational atherectomy followed by DCB has been shown to be safe in several case reports and case series, and CARDIAC study assessed its performance in a broader patient population (see below).

Several studies showed that combining RA with DCB is a feasible stent-less strategy for complex calcified lesions, as shown in Table 10.1 [25–32]. Li et al. in severely calcified lesions reported a TLR of 12.9% for DCB vs. 6.5% for DES ($p = 0.086$) and a MACE of 17.7% vs. 12.9% ($p = 0.290$) [26]. Similarly, Dong et al. showed that TLR at 12–30 months was comparable between DCB and DES after debulking by RA (13.79% vs 18.77%, $p > 0.05$) [27]. Takamura et al. observed no significant difference at 3 years follow up comparing RA and/or OA before DCB and DES implantation, with a TLR of 16.2% vs. 13.4% ($p = 0.843$) and MACE of 18.3% vs. 16.2% ($p = 0.13$) [32]. In contrast, Yui et al. in heavily calcified lesions at 1 year follow up observed TLR was higher in DCB compared to DES (10.2% vs 3.0%, $p = 0.001$) [31].

Orbital Atherectomy

Orbital atherectomy (OA) is an ablative technique used to prepare severely calcified or rich-

in-plaque coronary lesions, offering an alternative to RA. Unlike RA, where a diamond-tipped burr spins concentrically, OA uses an eccentrically mounted diamond-coated crown that spins at 80,000–120,000 rpm (Fig. 10.3). This mechanism creates a centrifugal force, which sands the calcified plaque, leaving softer tissue unaffected. OA can be performed bidirectionally, reducing the risk of entrapment—a known complication of RA. OA uses a single 1.25 mm crown, and larger lesions can be treated by increasing the speed or adjusting the rate of advancement. On average, a luminal diameter of 1.5 mm is achieved, with a potential of >2 mm with sequential passes at 1 mm/s. The sanding effect produces fine particulate debris (~2 μm), leading to low rates of no-reflow [56].

Orbital atherectomy (OA) followed by DCB has been evaluated in smaller Japanese cohorts. Mitsui et al. reported a 1-year MACE-free survival of 90.3% with OA + DCB in calcified de novo lesions, comparable to OA + DES [33]. Similarly, Takamura et al. found no significant differences in TLR or MACE at 3 years between atherectomy (RA/OA) followed by DCB versus DES, supporting the feasibility of OA + DCB in selected patients [32].

Directional Coronary Atherectomy and DCB

Directional coronary atherectomy (DCA) is a tool only available in a few countries, including Japan, and its experience is limited.

DCA followed by DCB has been explored primarily in left main and bifurcation lesions. In a Japanese multicenter retrospective registry, Kitani et al. reported outcomes of DCA + DCB in 129 patients with coronary bifurcation lesions, demonstrating 1-year TVF and TLR rates of 10.9% and 3.1%, respectively. Similarly, Kobayashi et al. reported 1-year MACE and TVF rates of 10.5%, while Murai et al. demonstrated higher TLR and smaller luminal gain with DCA + DCB compared with DCA + DES at 5 years, suggesting limitations of this strategy in complex bifurcation anatomy [34–36].

Excimer Laser Coronary Atherectomy and DCB

Excimer laser coronary atherectomy (ELCA) facilitates debulking of complex or non-crossable coronary lesions using a pulsed ultraviolet laser catheter. ELCA achieves plaque modification by atherosclerotic components, including calcium and fibrous tissue [57–60]. The procedure is dependent on laser wavelength,

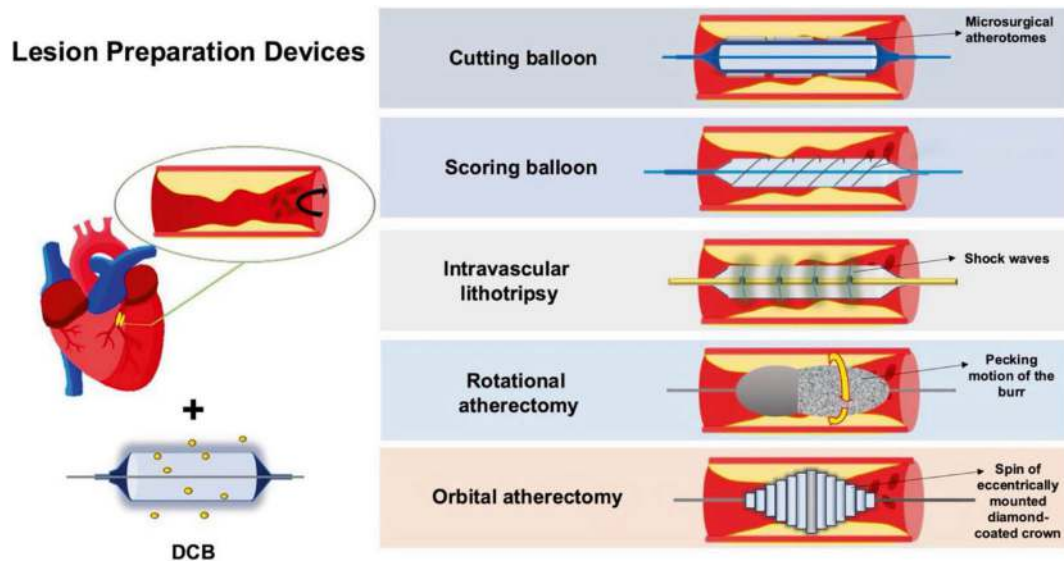


Fig. 10.3 Lesion preparation specialty devices before DCB inflation

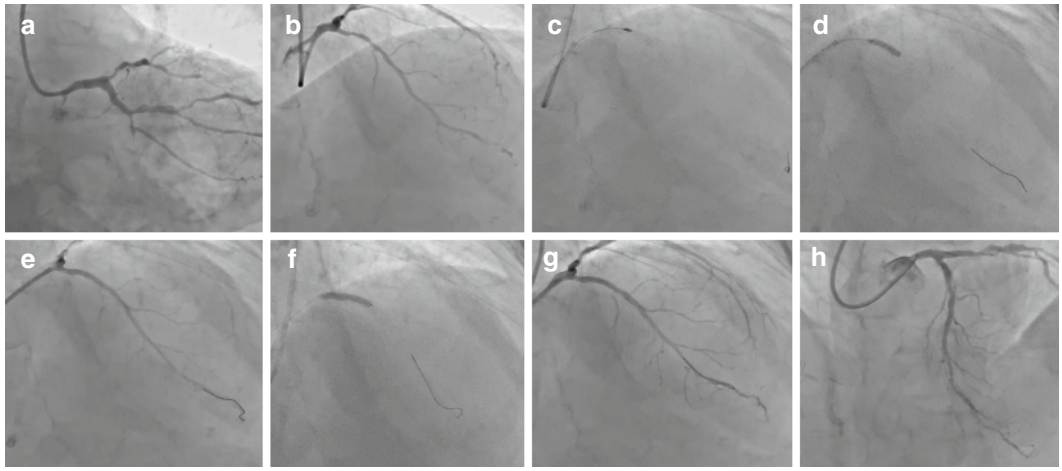


Fig. 10.4 DCB angioplasty after Rotational Atherectomy and Intravascular Lythotripsy: (**a**, **b**): baseline angiograms showing a calcific proximal left anterior descending artery (impossible to cross with intravascular imaging and Intravascular Lythotripsy); (**c**): Rotational Atherectomy with 1.5 mm burr; (**d**): Intravascular Lythotripsy with a 3.0/12 mm balloon; (**e**): result after lesion preparation, including a 3.0 mm non-compliant balloon; (**f**): DCB deployment (3.0/20 mm); (**g**, **h**): final angiographic result. (From Levin et al. [61]. Copyright 2004, National Academy of Sciences, USA)

whereby shorter wavelengths generate less heat, result in shallower tissue penetration, and lesser tissue modification. ELCA induces atherosclerotic ablation through three mechanisms, which are photochemical, photothermal, and photomechanical. Clinically, ECLA has been shown to be effective when coronary lesions are resistant to conventional balloon angioplasty [57–60].

ELCA followed by DCB has shown consistent benefits in ISR and acute coronary syndrome settings [60, 62]. In prospective and retrospective studies, ELCA+DCB was associated with lower TLR compared with DCB alone, without excess periprocedural complications [41–43]. In STEMI and ACS populations, ELCA+DCB demonstrated acceptable angiographic durability and safety, although some studies reported higher TVR compared with stent-based strategies [44, 45]. All studies showing ELCA for debulking before DCB are shown in Table 10.1 [41–47].

In conclusion, atherectomy techniques as tools in specific lesion settings before DCB are effective for treating calcified coronary lesions, with procedural success and patient outcomes dependent on operator expertise and appropriate patient selection.

4. Intravascular lithotripsy

IVL utilizing balloon-based technologies like the Shockwave IVL (USA) is a promising treatment for coronary artery calcifications (Figs. 10.3 and 10.4). The procedure involves a balloon inflated to low pressure, emitting electrical energy to create vapor bubbles that produce acoustic waves, which modify calcified plaque.

Several studies have shown the safety of the application of this technique before DCB use in the femoro-popliteal segment (please see the dedicated Chaps. 21 and 22 in this Book).

In the coronary arena, a *crack-and-drug strategy* where IVL is applied before DCB was tested in a study exploring such strategy against IVL followed by DES implantation. The study population was derived from the BENELUX-IVL registry in which the primary safety endpoint was in-hospital MACE, including cardiac death, non-fatal myocardial infarction, or TVR [37]. The final population of 45 patients (including ISR) treated with this technique showed similar intra-procedural complications between DCB and DES (5.8% vs. 8.9%, $p = 0.41$), no need for bail-out stenting, and similar procedural success (92%

vs. 89%, $p = 0.55$) and in-hospital MACE (2% vs 0%, $p = 0.33$) [37].

Another small study from France also addressed the in-hospital and short-term outcome following IVL + DCB in 14 patients. After 1 month, there were no cases of acute vessel occlusion, TLR, or cardiac death, with two cases of TLR occurring between 1 and 6 months [40]. Studies using IVL for lesion preparation before DCB are summarized in Table 10.1 [37–40].

CARDIAC Study

The CARDIAC trial presented in 2026 (D. Benedetto, oral presentation) showed that the use of different lesion modification devices like RA, OA, or IVL followed by DCB is feasible and associated with good safety and efficacy at 1 year. Of the 121 patients with de novo severely calcified coronary artery lesions who underwent solo-DCB treatment, plaque modification was performed with RA, 37%, OA, 17%, and/or Shockwave IVL, 53%. Notably, 6% of procedures involved a combination of RA + SW or OA + IVL. All patients received subsequent predilatation with semi-compliant or non-compliant balloons. The procedural success rate was 100%, with no major complications such as vessel perforation. Angiographic vessel dissection occurred in 21% of cases. Additionally, three patients experienced slow flow after DCB inflation, all successfully managed with intracoronary pharmacological treatment. After a median follow-up of 384 days (IQR 185–453), TLF occurred in 6.6% of patients with no cardiac deaths, 1.7% of nonfatal MI, and 5% TLR.

The findings of CARDIAC suggest the safety and efficacy of aggressive lesion preparation and subsequent restenosis inhibition through DCB treatment, in a selected patient population with severely calcified coronary lesions.

10.3.2 Why Are Non-Flow-Limiting Dissections Left Untreated? "Audentes Fortuna iuvat"

Leaving a dissection after balloon angioplasty is quite common. If historical data show that this occurs in 10–20% as per angiographic parameters, intravascular imaging is showing that any final degree of dissections occurs in >95% of the DCB cases.

A study done by Cortese et al. [63] aimed to underline the clinical and angiographic outcomes of non-flow-limiting dissections left after DCB angioplasty, out of 48 patients left with untreated dissections. Complete vessel healing at angiography was observed in 45 patients (93.8%). This study confirmed for the first time that an untreated, not flow-limiting (types A-C) dissection after DCB with paclitaxel should be considered safe, with potential increase in drug uptake and improved late lumen enlargement, like other studies later showed [64]. The concept of untreated dissection was also tested after sirolimus-coated balloon angioplasty. In a subanalysis of the EASTBOURNE study in which ScB was used in all comers with de novo lesions, this balloon showed a favorable result with no cases of acute or sub-acute occlusions in the not flow-limiting dissection arm [65].

Similarly, a recent study evaluated the incidence, predictors, and outcomes of coronary dissections following DCB angioplasty for de novo CAD. Among 522 DCB-treated lesions in 466 patients, 39.1% had angiographic dissections, with 21.1% requiring bailout stenting and 78.9% left untreated. Dissection incidence increased from type A to type E ($p < 0.001$), with left anterior descending artery involvement being a significant risk factor (OR 1.64, 95% CI: 1.12–2.39). At 2 years, TLF was as low as 2.7% for untreated dissections and 4.2% for lesions without dissection ($p = 0.324$). These results suggest that while dissections are common after DCB angioplasty, they do not significantly impact mid-term clinical outcomes, highlighting that careful lesion preparation is crucial for managing dissections without increasing risk [66].

10.4 Future Studies

Despite the advancement in DCB technologies, lesion preparation remains *the cornerstone* for optimal long-term outcomes. There are ongoing

high-quality studies in which different techniques for lesion preparation are tested. The NATURE study (jRCTs032230543) is a randomized multicenter trial meant to explore CB in contrast to standard balloons in lesion preparation for de novo lesions before DCB. Like the recent SHORT-CUT trial, this study will be IVUS-guided, assuring precise balloon sizing and accurate evaluation for lesion preparation. There is a randomized multicenter controlled Australian SCORE-CUT DCB trial (ACTRN12625001349437) will test both ScB and CB against standard balloons for lesion preparation before DCB. Lesion preparation will be assessed by IVUS with a main focus on pre and post-MLA and plaque burden management.

10.5 A Proposed Algorithm for Optimal Lesion Preparation Pre-DCB

As depicted in this chapter, the efficacy of DCB is highly contingent upon meticulous lesion preparation, which optimizes drug delivery and reduces adverse procedural outcomes. This chapter delineates a comprehensive, evidence-based algorithm for lesion preparation pre-DCB, integrating the latest advancements and best practices from interventional cardiology.

The proposed algorithm by our group for PCI in ISR (Fig. 10.5) and de novo lesions (Fig. 10.6) integrates both conventional techniques and advanced imaging-guided strategies to optimize clinical outcomes. For ISR, *initial intravascular imaging* is recommended to identify the underlying mechanism of stent failure. If mechanical issues like stent under-expansion or malapposition are present, these should be addressed with balloon dilatation, utilizing specialized devices such as ScB, CB, or shockwave balloons, or excimer laser if required. Once mechanical issues are resolved, the algorithm suggests using ScB or CB prior to DCB therapy, provided there is no persistent recoil or flow-limiting dissection. In the presence of such dissection, a DES is preferred [67].

For de novo lesions, the approach depends on lesion complexity. In noncomplex lesions, predilatation with SC or NC balloons is typically sufficient. If post-dilatation results in recoil less than 30% and no flow-limiting dissection, DCB may be applied. In case of suboptimal results, intravascular imaging is recommended to evaluate the lesion, followed by the use of larger or specialized balloons if necessary. If optimal

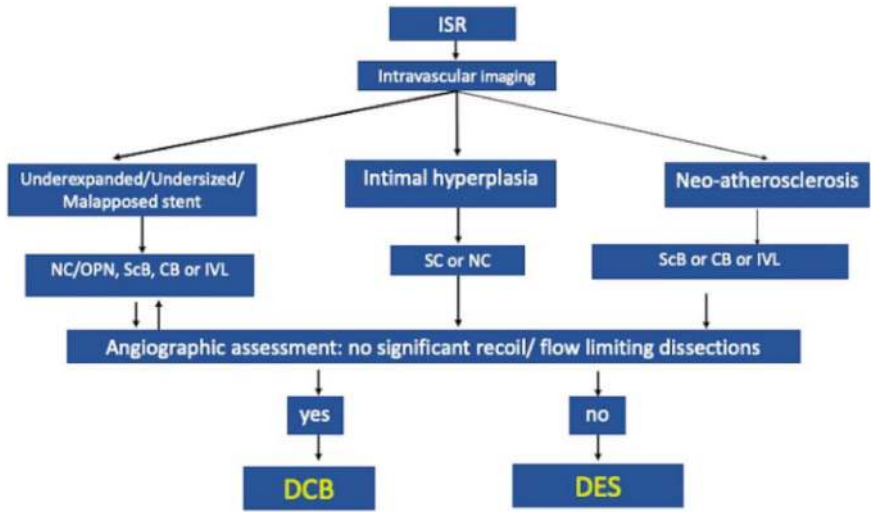


Fig. 10.5 Step-by-step algorithm when dealing with in-stent restenosis. (Reproduced from Basavarajaiah et al. [67], with permission)

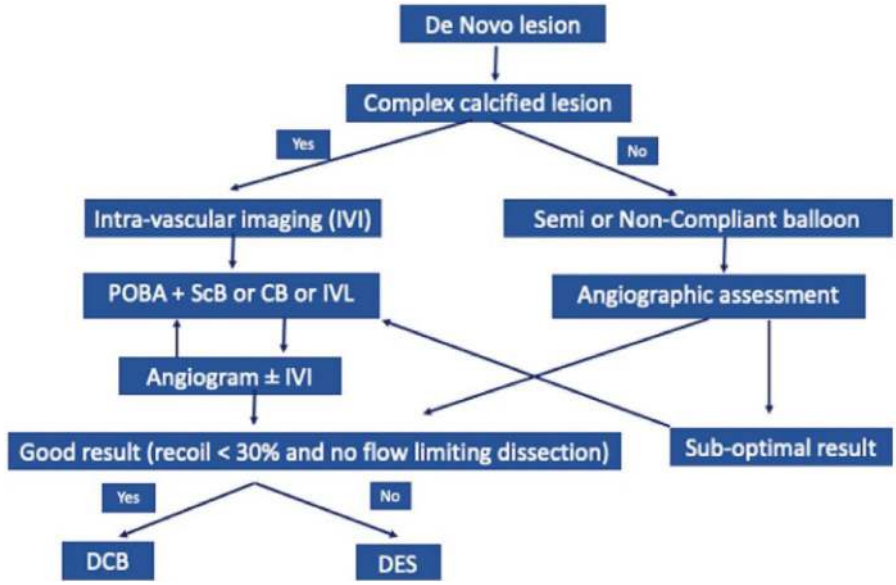


Fig. 10.6 Step-by-step algorithm when dealing with De Novo lesions. (Reproduced from Basavarajaiah et al. [67], with permission)

result is not achieved, stenting should be considered instead of DCB. On the other hand, for complex lesions, lesion preparation should always be guided by *intravascular imaging*, ensuring adequate modification before DCB therapy [67].

Once optimal lesion preparation is confirmed, DCB should be chosen based on the reference vessel size and inflated at nominal pressure for at least 60 s to ensure sufficient drug transfer to the vessel wall and obtain some scaffolding effect [68]. Post-procedural imaging, including angiography, confirms the success of the procedure, verifying that TIMI 3 flow has been restored. We have also shown that DCB inflation time was an independent negative predictor for bailout stenting in a multivariable logistic model in a broad population of patients, meaning that the more you inflate a DCB, the lower the risk of bailout stenting [69, 70].

This algorithm emphasizes that proper lesion preparation is essential for a successful DCB therapy, as inadequate modification or residual stenosis can impair drug diffusion and necessitate stenting. Advanced techniques such as specialized balloons and atherectomy improve vessel compliance and durable results. As technology advances, further refinements to this algorithm are expected to improve clinical outcomes.

10.6 Conclusions

Effective lesion preparation is critical prior to DCB angioplasty. Unlike stent placement, which benefits from the support of metallic scaffolding and the radial force, inadequate lesion preparation before DCB can lead to suboptimal angiographic and later clinical outcomes. Vessel preparation has evolved from a theoretical concept ("just predilate the lesion") to a core component of modern endovascular procedures, aiming to maximize lumen gain, optimize the vessel bed, and reduce dissection risks. Initial data suggest that ScB implementation for lesion preparation prior to DCB angioplasty in selected lesion types improves angiographic outcomes and reduces the risk of severe dissections, which require stent implantation. However, larger randomized controlled trials are required to validate the safety and effectiveness of optimal lesion preparation strategy before DCB angioplasty.

Key goals for optimal vessel preparation in DCB procedures include:

- Maximizing vessel lumen gain while avoiding barotrauma.
- Reducing plaque burden to facilitate drug uptake, particularly by addressing severe calcification.
- Achieving a lumen with less than 30% residual restenosis (or focal 40%, in case of long lesions).
- Preserving TIMI 3 flow.

Future directions include the development of new, deliverable vessel preparation tools and a better understanding on when we should apply these optimal preparation tools and techniques.

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11 The Use of Drug-Coated Balloons for Patients with In-Stent Restenosis

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11.1 Mechanisms of In-Stent Restenosis

In-stent restenosis (ISR) remains the leading cause of stent failure, accounting for 5–10% of percutaneous coronary interventions (PCIs) in contemporary clinical practice [1, 2]. Importantly, the ongoing growth in PCI volumes, combined with the progressive aging of treated patients and the increasing complexity of coronary lesions, is expected to further amplify the incidence of ISR [3].

Understanding the underlying mechanisms of ISR is crucial for effective treatment, including the development of targeted strategies for lesion preparation. The risk factors for ISR can be classified into three categories: clinical, anatomical, and procedural [2, 4] (Fig. 11.1). Clinical risk factors include female sex, advanced age, obesity, and comorbid conditions such as diabetes mellitus (DM) and chronic kidney disease (CKD). Anatomical risk factors identified in angiography include heavily calcified or long lesions, bifurcations, ostial lesions, chronic total occlusions (CTO), small-vessel disease, multivessel coronary artery disease, and interventions involving ISR lesions or saphenous vein grafts. These characteristics may lead to suboptimal

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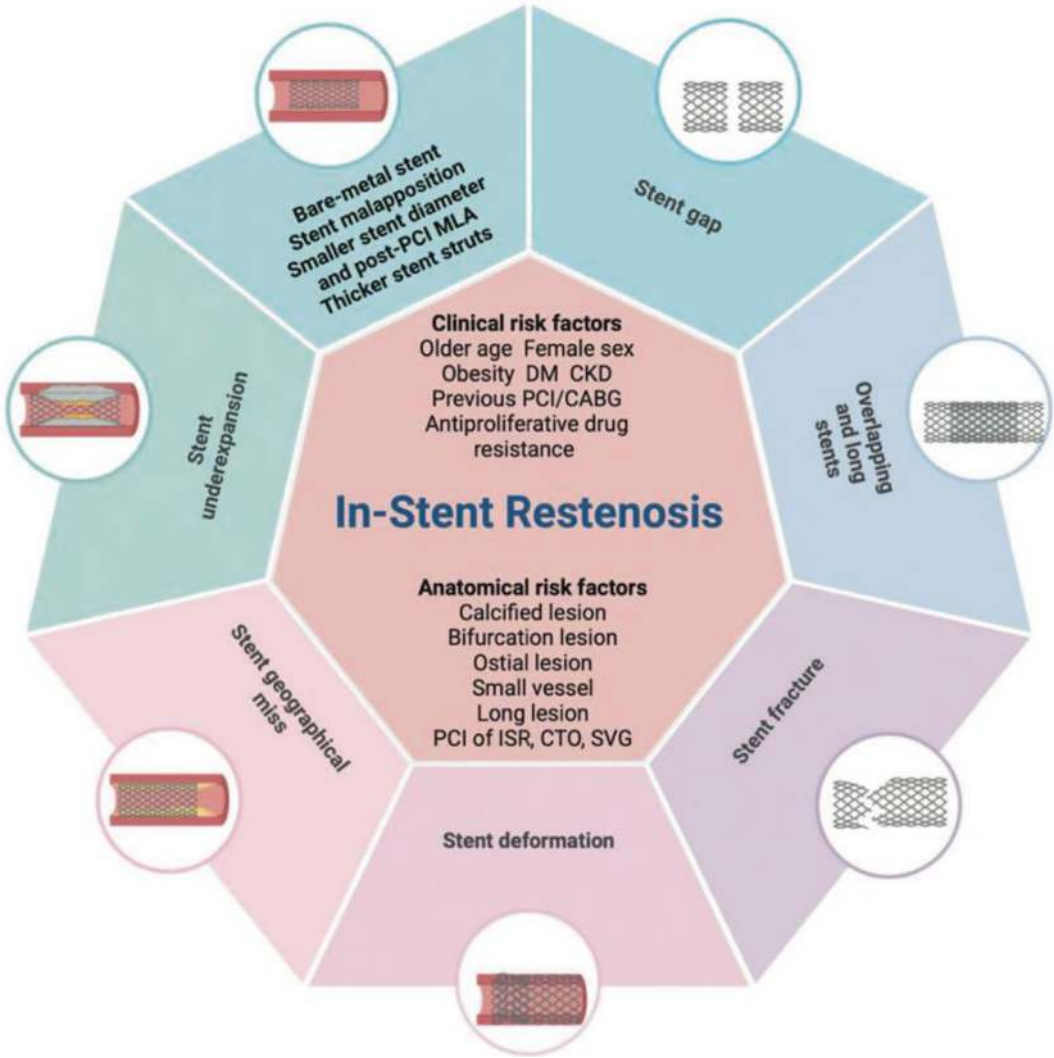


Fig. 11.1 Clinical, procedural, and anatomical factors associated with ISR. (From [4]). *Abbreviations*: CABG, coronary artery bypass graft; CKD, chronic kidney disease; CTO, chronic total occlusion; DM, diabetes mellitus; ISR, in-stent restenosis; MLA, minimum lumen area; PCI, percutaneous coronary intervention; SVG, saphenous vein graft

procedural outcomes and subsequently increase the risk of ISR [2]. Procedural factors contributing to ISR include stent malapposition, underexpansion, geographic miss, stent deformation or fracture, overlapping stents, stent gaps, edge dissection or edge-related plaque burden, and the presence of multiple stent layers [2]. Consequently, an effective treatment strategy should address the underlying causes of ISR while optimizing systemic therapies to manage clinical risk factors adequately.

11.1.1 Clinical Factors

Comorbidities significantly influence the ISR process, and the underlying mechanisms are complex, ultimately contributing to the progression of atherosclerosis. One of the strongest independent predictors of restenosis is DM [5]. Endothelial damage is a major factor in both microvascular and macrovascular complications, primarily due to oxidative stress induced by hyperglycemia [6, 7]. Furthermore, the hyperac-

tivity of vascular smooth muscle cells and the impairment of specific glycoproteins lead to more aggressive and rapidly progressing atherosclerosis. CKD is also associated with an increased risk of ISR, mostly due to a higher burden of comorbidities in CKD patients, as well as more complex CAD, which includes a greater prevalence and severity of coronary artery calcification [8, 9]. Moreover, in both DM and CKD patients, vessel trauma caused by stent implantation promotes intimal hyperplasia, resulting in luminal loss, reduced minimal luminal area, and subsequent target lesion revascularization (TLR) [10].

11.1.2 Anatomical and Morphological Factors

Coronary artery calcification is a significant anatomical risk factor for ISR. Lesion calcification increases with age and remains the main reason for stent underexpansion. Several factors contribute to coronary calcification, including hyperphosphatemia, calcium-phosphate imbalance, uremic toxins, chronic inflammation, oxidative stress, and the activation of various signaling pathways in different cell types, such as vascular smooth muscle cells, macrophages, and endothelial cells. Importantly, coronary artery calcification independently predicts the risk of coronary heart disease and total cardiovascular disease, often surpassing traditional risk factors in predictive value.

Calcified nodules (CN), which can be classified as eruptive and non-eruptive, play a crucial role in the ISR mechanism. Non-eruptive CN tend to be resistant to dilation and are associated with suboptimal procedural results. A study by Teda et al. [11] identified CNs in 5% of ISR lesions. Other forms of calcified lesions include severe circumferential coronary calcification with a 360° distribution (napkin ring appearance). Such lesions, if not appropriately prepared with the presence of calcium cracks, increase the risk of stent underexpansion. Deploying DES without first addressing circumferential calcification exposes patients to a long-term risk of ISR [12]. Consequently, the selection of treatment strategy, particularly regarding lesion preparation, should be guided by an assessment of the severity and distribution of calcifications, evaluated using intracoronary imaging.

Another anatomical risk factor for ISR is the presence of bifurcation lesions. Coronary artery bifurcation disease is found in at least 20% of patients undergoing coronary angiography [13]. Bifurcation lesions significantly contribute to the risk of ISR; however, the level of the risk depends on the treatment technique used. Chen S et al. [14] showed that the ISR rates in the main vessel at the 13-month angiographic follow-up were comparable between the double-kissing crush (DK crush) strategy and provisional stenting. However, the ISR rate at the ostium of the side branch (SB) was 12.0% with provisional stenting, compared to 5.0% with the DK crush technique. Additionally, the DKCRUSH-II trial [15] found significantly lower angiographic restenosis rates at 8 months in the double-kissing group compared to the provisional stenting group. Specifically, the rates of ISR for the main vessel were 3.8% versus 9.7%, respectively ($p < 0.036$), and for the SB, the rates were 4.9% versus 22.2%, respectively ($p < 0.001$).

Revascularization of CTO lesions with DES implantation is associated with a higher rate of ISR during long-term follow-up [16]. The causes may be multifactorial, including stent undersizing or stent underexpansion. In a CTO-specific study, Kang et al. [17] found that the minimal lumen diameter (MLD) and stent expansion ratio were independent predictors of ISR. Moreover, optimizing the stent implantation based on intracoronary imaging enables obtaining the greatest MLD and stent expansion ratio to prevent downstream stent thrombosis and ISR. Furthermore, if the CTO is located at the aorto-ostium or a bifurcation, procedural complexity increases, resulting in a higher risk of long-term major adverse cardiovascular events (MACE) and ISR [18]. Finally, long lesions require the use of long or overlapping stents and total stent length is associated with an increased restenosis risk. Likewise, in small vessels, just a moderate neointimal growth can be enough to compromise the lumen, causing ISR.

11.2 Limitations of Drug-Eluting Stents

Drug-eluting stents (DES) significantly reduced the incidence of restenosis compared with bare-metal stents (BMS). However, the use of a permanent metal scaffold with a polymer-drug coating carries biological and mechanical limitations. These foreign bodies account for a small but persistent risk of target lesion failure (TLF) beyond the first year. These concerns are particularly relevant in the context of "leave nothing behind" strategies and explain the growing clinical interest in drug-coated balloons (DCB), especially in specific clinical settings [4].

A crucial limitation of DES is its sensitivity to the effectiveness of the implantation process. Stent underexpansion is identified as a significant factor contributing to DES failure and remains the strongest predictor of ISR. Intravascular imaging studies demonstrated that the majority of ISR events are associated with stent underexpansion. An analysis using intravascular ultrasound (IVUS) conducted by Kang et al. found that 42% of ISR lesions exhibited signs of underexpansion [19]. The other common mechanism is severe calcification, which often requires specialized techniques to modify the atherosclerotic plaque. In ISR associated with stent underexpansion, the combined presence of severe calcification and metal layer makes achieving optimal lesion preparation particularly challenging. Consequently, implanting a second stent can lead to persistent underexpansion, which in turn increases the incidence of adverse events [20].

The implantation of DES leaves behind a permanent metallic layer. In patients with recurrent restenosis or requiring the use of overlapping stents, additional metal layers promote neointimal proliferation, thereby increasing the risk of restenosis [21]. Studies have shown that the risk of ISR increases with the number and length of stents implanted, as well as with the use of tandem stenting. Furthermore, multilayer stent implantation may reduce the luminal area of the vessel, complicate future interventions, and increase the likelihood that subsequent devices will be underexpanded if the underlying mechanical problem is not addressed.

Although modern DES have improved safety profiles, late (acquired) malapposition remains clinically relevant and has been associated with DES failure, including thrombosis and restenosis [22]. Observational and mechanistic studies also link incomplete stent apposition with very late stent thrombosis [23]. These results demonstrate that permanent scaffolds remain susceptible to long-term biological and mechanical forces, such as vessel remodeling, recoil, and flow disturbances, which may lead to long-term stent failure despite initial PCI success. Another potential concern after DES implantation is delayed arterial healing, characterized by fibrin retention and incomplete endothelial coverage, both of which may increase the risk of late thrombosis [24]. Finn et al. highlighted that delayed coverage of the stent struts is a significant risk factor for late DES thrombosis. Although newer-generation platforms have reduced this risk, the presence of a polymer or drug-coated foreign material continues to pose a major limitation, as it can affect the healing response [25].

DES incorporates a metal scaffold, a polymer, and a drug, which can lead to inflammatory reactions and hypersensitivity to its components. Early safety discussions and experimental observations also pointed out issues such as incomplete healing and inflammatory tissue reactions [26]. Clinical observations suggest that contact allergies to metals, such as nickel, are linked to ISR, indicating that the biocompatibility of the implant may be clinically important for certain patients [27]. Finally, neoatherosclerosis remains a frequent cause of ISR despite the use of new generation DES.

11.3 Potential Advantages of Drug-Coated Balloons

In coronary ISR, DCB offers an effective antiproliferative treatment while avoiding the need for an additional metal layer. DCB, after adequate vessel preparation, effectively treats intimal

hyperplasia. Furthermore, delivering an antiproliferative drug directly to the coronary artery wall without the need for an additional stent significantly reduces the risk of vessel thrombosis [28]. Moreover, there is also a theoretical advantage of DCB if shortening the duration of dual antiplatelet in high bleeding risk patients is a necessity or a therapeutic goal [29]. Moreover, this approach may preserve side branches, maintain vessel compliance, and theoretically simplify future interventions. DCB avoids the incremental risks of late stent thrombosis, neoatherosclerosis, and malapposition that increase with the addition of multiple stent layers. Using DCB as the initial revascularization strategy of ISR seems to be a reasonable approach. Importantly, this strategy, by not applying a second or third DES layer, allows DCB to retain the option for future DES placements [4].

11.4 Current Evidence on the Use of Drug-Coated Balloons in Patients with In-Stent Restenosis

DES represents the most widely adopted strategy in contemporary PCI [30]. Although DES have substantially reduced neointimal proliferation compared to BMS, they are not immune to ISR [1–4]. The expanding use of DES in patients with complex clinical profiles and adverse anatomical characteristics largely explains why DES-ISR remains a significant and unresolved clinical challenge, even though BMS-ISR is still encountered in routine practice [31]. In this context, defining the role and effectiveness of DCB is of paramount clinical relevance.

11.4.1 Drug-Coated Balloons Versus Plain Old Balloon Angioplasty

Randomized evidence has clearly demonstrated the superiority of DCB over plain old balloon angioplasty (POBA) for the treatment of ISR. In a preliminary randomized controlled trial (RCT) involving 50 patients with limus-DES-ISR, DCB angioplasty achieved significantly better angiographic outcomes than POBA, with a notable reduction in late lumen loss (LLL) (0.18 ± 0.45 vs 0.72 ± 0.55 mm; $p = 0.001$). This angiographic advantage translated into a significantly lower incidence of recurrent binary restenosis (8.7% vs 62.5%; $p = 0.0001$) and TLR (4.3% vs 41.7%; $p = 0.003$) [32]. Subsequently, a multicenter RCT enrolling 110 patients with ISR after any type of DES confirmed the superior efficacy of DCB compared with POBA [33].

More robust long-term evidence was provided by the ISAR-DESIRE 3 trial, in which 137 patients with DES-ISR were randomized to paclitaxel-coated balloon (PCB) angioplasty and 134 patients to POBA. At 10-year follow-up, the device-oriented composite endpoint (DOCE) occurred in 55.9% of patients treated with PCB compared with 72.0% in the POBA group (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.42–0.78), with a concomitant significant reduction in TLR in the DCB arm (43.9% vs 58.0%; HR 0.57, 95% CI 0.40–0.81; $p = 0.001$) [34].

Consistent findings were recently reported in the AGENT IDE trial, a multicenter, randomized, single-blind study comparing PCB with POBA in 600 patients with coronary ISR. Of note, until 2024 the FDA did not approve the use of DCB in the coronary space in the USA, and therefore POBA was considered a reasonable comparative strategy for patients with ISR. At 1 year, TLF occurred significantly less frequently in the DCB group (17.9% vs 28.6%; HR 0.59, 95% CI 0.42–0.84), driven primarily by lower rates of ischemia-driven TLR and target vessel myocardial infarction (MI) [35]. These benefits persisted at 2 years, with TLF rates of 27% in the DCB group versus 34% with balloon angioplasty (HR 0.73) and an almost twofold higher risk of repeat TLR among patients treated with POBA [36].

11.4.2 Drug-Coated Balloons Versus Drug-Eluting Stents

Comparisons between DCB and repeat DES implantation for the treatment of ISR remain controversial, with most available evidence derived from studies evaluating PCB.

The PEPCAD China ISR trial was a prospective, multicenter, single-blind randomized study that enrolled 220 patients with DES-ISR, randomized 1:1 to PCB angioplasty or DES implantation. The primary endpoint, in-segment LLL at 9 months, demonstrated noninferiority of PCB compared with DES. Rates of binary restenosis, TLF, and MACE at 12 months were similar between the two strategies [37]. Long-term follow-up from the ISAR-DESIRE 3 trial confirmed these findings, with no statistically significant differences at 10 years between PCB and DES in DOCE (55.9% vs 62.4%, p = 0.610) and TLR (43.9% vs 38.6%, p = 0.282) [34]. The RIBS V trial was a prospective, multicenter, randomized study including 189 patients with BMS-ISR, allocated to treatment with DCB or DES. The primary endpoint, in-segment MLD at 9-month follow-up, was significantly larger in the DES group compared with the DCB group. However, clinical outcomes at 1 year were comparable, with similarly low rates of MACE between groups (8% in the DCB group vs. 6%in the DES group; p = 0.60) [38].

In contrast, the RIBS IV RCT demonstrated a differential efficacy between DCB and DES in the more challenging setting of DES-ISR. In this prospective multicenter study enrolling 309 patients with DES-ISR, DES implantation resulted in superior angiographic outcomes, that translated into improved clinical outcomes: at 3 years, MACE occurred less frequently in the DES group than in the DCB group (12.3% vs 20.1%; HR 0.57, p = 0.04), driven primarily by lower rates of TLR (7.1% vs 15.6%, p = 0.015). Rates of cardiac death, MI, and stent thrombosis remained low and comparable between groups [39] (Fig. 11.2). These results were subequently confirmed by the DAEDALUS individual patient–level meta-analysis, which included 1976 patients from 10 RCTs. At 3-year follow-up, DCB and DES showed comparable efficacy and safety in BMS-ISR, whereas in DES-ISR, DCB was associated with a significantly higher risk of TLR compared with DES (20.3% vs 13.4%; HR 1.60, p = 0.002) [40]. However, a safety signal in favor of DCB emerged in this study in patients with ISR treated with first-generation DES that was not present in patients treated with new-generation DES. Based on these data, the 2024 European Society of Cardiology guidelines for chronic coronary syndromes recommend the use of DES over DCB for the treatment of DES-ISR, with a substantial downgrade of DCB from the previous guidelines [41].

Contemporary real-world evidence complements randomized data. In a nationwide registry analysis from the Swedish SCAAR, including 9062 patients treated for ISR and followed up for 5 years, DCB was associated with a higher risk of TLR (adjusted HR 1.20, [95% CI, 1.06–1.37], p = 0.005) compared with DES, while rates of all-cause death, cardiovascular death, MI, and repeat PCI were similar across strategies. These results were consistent across ISR subtypes, including DES-ISR and BMS-ISR [42]. Similarly, in the DRAGON registry, Wańha et al. evaluated long-term outcomes of DCB versus thin-strut DES in 846 patients with DES-ISR presenting with chronic coronary syndrome. Over a median follow-up of approximately 3 years, DES implantation was associated with significantly lower rates of TLR and DOCE compared with DCB, both in crude and propensity score–matched analyses, while rates of MI and cardiovascular death were comparable between groups [43, 44].

In recent years, sirolimus-coated balloons (SCB) were developed to address some potential limitations of PCB, including the narrow therapeutic window and concerns related to cytotoxicity and coronary distal embolization. Limus drugs are not lipophilic, and achieving adequate

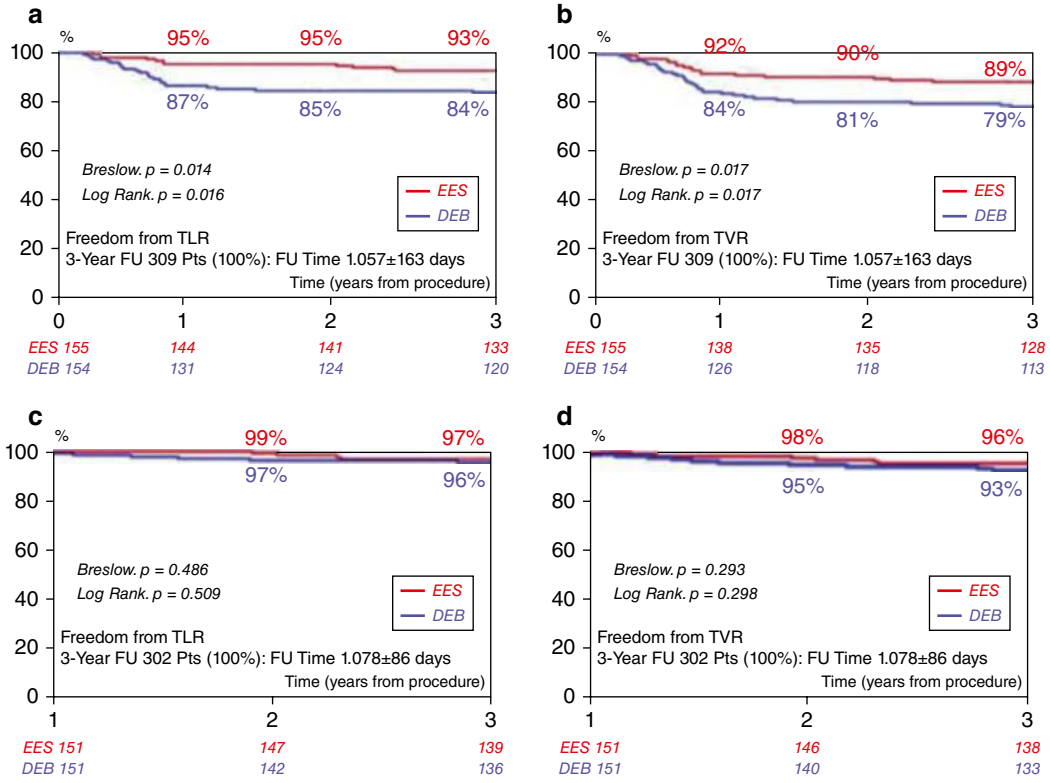


Fig. 11.2 Kaplan-Meier curves for DCB vs. DES in the RIBS IV trial. (From [50]). (**a**) Freedom from TLR. (**b**) Freedom from TVR. (**c**, **d**) Landmark analyses (events beyond the first year). *Abbreviations*: DEB: drug-eluting balloons; EES: everolimus-eluting stents; TLR: target lesion revascularization; TVR: target vessel revascularization

transfer and retention at the vessel wall is more challenging. However, contemporary SCB platforms incorporate advanced drug-delivery technologies designed to optimize arterial uptake and retention. For instance, the Magic Touch SCB (Concept Medical, Tampa, US) employs Nanoluté nanocarriers, whereas the Selution SCB (MedAlliance, Nyon, Switzerland) incorporates sirolimus into biodegradable polymer micro-reservoirs [45].

Clinical evidence supporting the use of SCB for ISR continues to expand. In pooled analyses from the EASTBOURNE and DEB-DRAGON registries, including 1545 patients with ISR, clinical outcomes following treatment with the Magic Touch SCB were comparable to those achieved with thin-strut DES implantation at 24-month follow-up [46] (Fig. 11.3). More recently, the SELUTION4ISR RCT enrolled 418 patients with coronary ISR, who were randomized to treatment with the Selution SLR SCB or a standard-of-care strategy (repeat DES implantation [80%] or POBA [20%]). At 1 year, the primary endpoint of TLF occurred in 15.2% of patients treated with SCB and 13.5% of those treated with standard of care, meeting the prespecified criterion for noninferiority. However, TLF was higher in patients treated with SCB as compared with patients treated only with DES. Rates of clinically driven TLR were also similar between groups (11.9% vs 11.5%), with no significant differences observed [47].

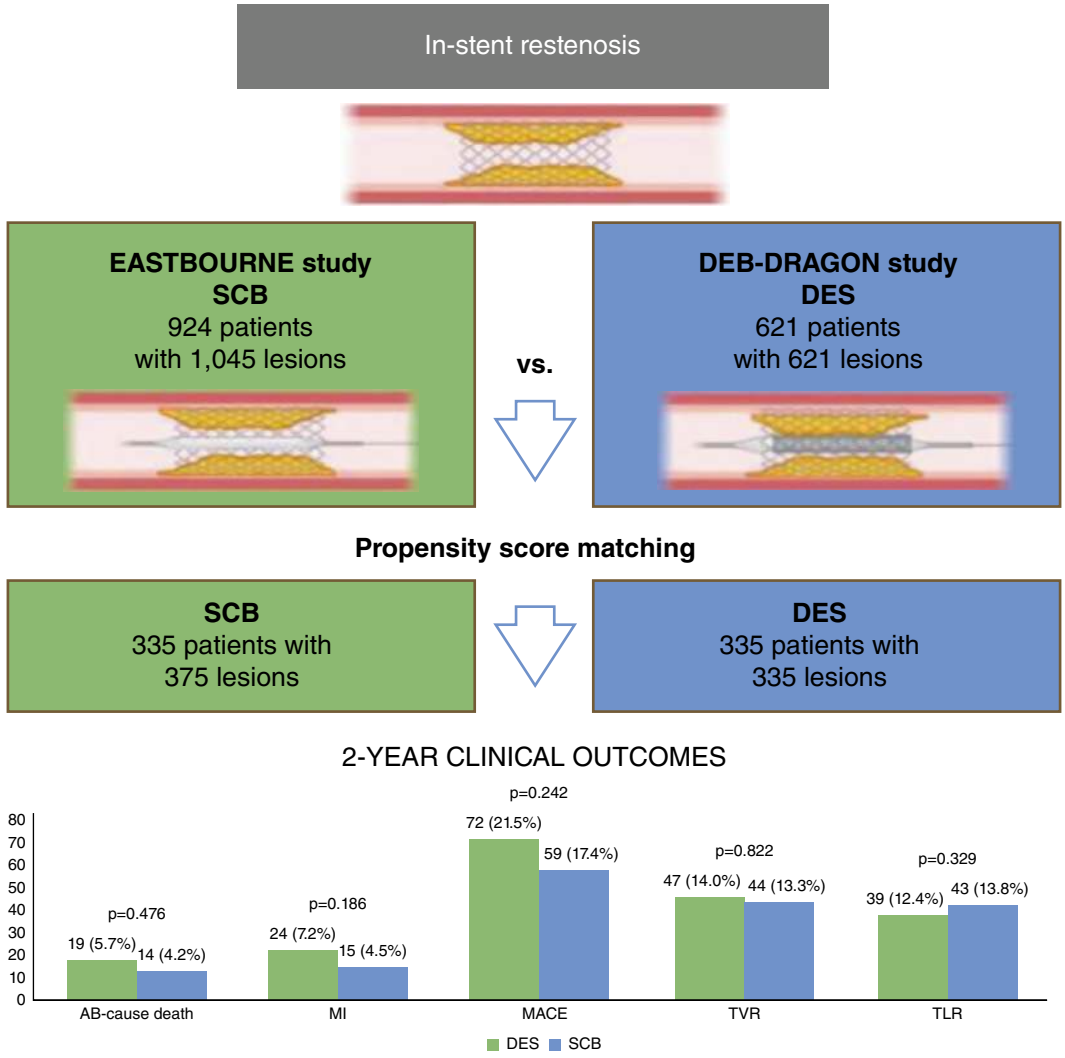


Fig. 11.3 Clinical outcomes of SCB vs. DES in ISR. (From [46]). *Abbreviations*: DES: everolimus-eluting stents; SCB: sirolimus-coated balloons

11.4.3 Paclitaxel-Coated Balloons Versus Sirolimus-Coated Balloons in ISR

Head-to-head RCTs comparing limus-DCB with PCB are small and have short clinical follow-up. In a recent meta-analysis including RCT of patients with de novo lesions or ISR, limus-DCB were inferior to PCB regarding late angiographic parameters, with a smaller MLD (standardized mean difference (SMD): 0.14; 95% CI: 0.27 to 0.01; $p = 0.03$) and a higher risk of LLL (SMD: 0.18; 95% CI: 0.08–0.27; $p = 0.001$) and binary restenosis (50% vs % $p = 0.0002$) [48]. However, long-term clinical outcomes were similar with the two drugs. The late lumen enlargement phenomenon may be implicated in these findings, but this phenomenon appears to have a limited influence on clinical outcomes ofpatients treated for ISR [49].

The SIBLINT-ISR trial enrolled 258 patients with ISR, who were randomized 1:1 to treatment with PCB or SCB after successful lesion preparation. In-segment LLL at 9 months was comparable

between the two groups, and no significant differences were observed in TLF at 12-month follow-up [50] (Fig. 11.4). Similarly, the TIS-2 randomized controlled trial included 145 patients with ISR, who were randomized 1:1 to SCB or PCB angioplasty. Rates of binary restenosis (31.6% vs 30.4%) and 12-month MACE (31% in both groups) were comparable between treatment strategies [51].

These findings were corroborated by real-world evidence. In an Italian study evaluating different DCB platforms, 12-month TLR rates were similar between SCB and PCB (12.1% vs 11.4%; adjusted HR 1.05, 95% CI 0.72–1.54) [52]. Likewise, MACE rates did not differ significantly (18.3% vs 17.6%; adjusted HR 1.03, 95% CI 0.76–1.41). Finally, in a pooled analysis of the EASTBOURNE and PEARL registries, including 1292 patients treated for ISR, clinical outcomes were comparable between SCB and PCB. At 1 year, the risk of MACE was similar in SCB-treated and PCB-treated patients (17.8% vs 14.1%; adjusted HR 1.17, 95% CI 0.80–1.70; $p = 0.40$) [53].

11.4.4 Future Studies

The optimal revascularization strategy for patients with ISR, whether to implant an additional scaffold or to adopt a DCB–based approach, remains an open clinical question. A key challenge lies in the substantial heterogeneity of ISR, which encompasses diverse restenotic mechanisms and morphological patterns. Moreover, differently from DES, for DCB a class effect does not exist, as individual devices differ markedly in their antirestenotic drug, coating technology, and delivery platform, all of which may affect clinical efficacy. Therefore,

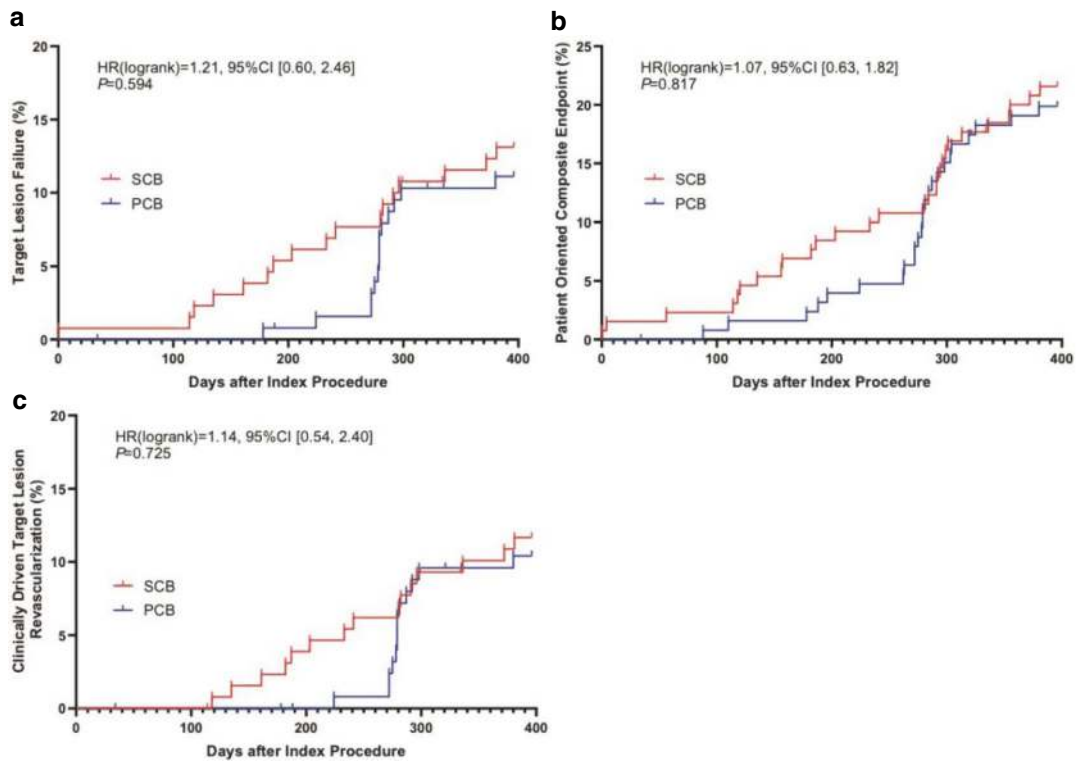


Fig. 11.4 Kaplan-Meier curves of 1-year clinical outcomes for patients who received SCB vs. PCB in the SIBLINT trial. (From [39]). (**a**) target lesion failure; (**b**) patient-oriented composite endpoint; (**c**) target lesion revascularization. *Abbreviations*: PCB: paclitaxel-coated balloons; SCB: sirolimus-coated balloons

Table 11.1 Ongoing randomized studies on DCB for ISR

Study name	Study Population	Inclusion criteria	DCB type	Comparison group	Primary endpoint
MAGICAL ISR (NCT05908331)	492 patients with DES-ISR	RVD >2.0 and ≤4.0 mm Target lesion length ≤36 mm Successful lesion preparation	MagicTouch SCB (Concept Medical, Tampa, US)	POBA	TLR at 12 months
ISAR-DESIRE 5 [54]	376 patients with DES-ISR	>50% angiographic DES restenosis OCT-derived classification of neointimal morphology (homogeneous vs non-homogeneous)	All-comer DCB	Repeat DES	MACE (all-cause death, MI, TLR) at 24 months
Prevail Global [55]	730 patients with ISR	RVD >2.0 and ≤4.0 mm Target lesion length ≤26 mm TIMI flow? 2	Prevail PCB (Medtronic, Santa Rosa, US)	Agent PCB (Boston Scientific, Natick, US)	TLF (cardiac death, target vessel MI, TLR) at 12 months
UNIQUE DCB-II (NCT04119986)	220 patients with ISR	QFR <0.8 of target lesion in the coronary stent	All-comer DCB	Repeat DES	LLL at 12 months

Table legend. *DES* drug-eluting stents, *MI* myocardial infarction, *ISR* in-stent restenosis, *LLL* late lumen loss, *OCT* optical coherence tomography, *POBA* plain old balloon angioplasty, *QFR* quantitative flow ration, *RVD* reference vessel diameter, *TLF* target lesion failure, *TLR* target lesion revascularization

ongoing RCTs are expected to further refine PCI strategies and device selection across distinct ISR phenotypes, ultimately supporting a more personalized and mechanism-driven approach to ISR management [54, 55] (Table 11.1).

11.5 Practical Considerations

11.5.1 Intracoronary Imaging

Available evidence consistently supports a meaningful role for intracoronary imaging in ISR management. In the RIBS III trial, IVUS guidance, used at operator discretion in 38% of patients, was associated with greater acute lumen gain and a larger MLD at 9-month angiographic follow-up [56]. More robust prognostic evidence comes from the iOPEN-ISR registry, which included 1522 patients and demonstrated significantly lower 1-year MACE rates with IVUS-guided compared with angiography-guided ISR PCI (14.1% vs 18.0%, $p < 0.001$) [57]. Similarly, a retrospective study in DES-ISR reported a marked reduction in 2-year MACE with optical coherence tomography (OCT)-guided versus angiography-guided intervention (7% vs 15%, $p = 0.007$) [58]. Additional mechanistic insights were provided by the RESTO registry, where pre-procedural OCT led to a change in treatment strategy in approximately 30% of ISR cases and identified stent underexpansion as a strong predictor of subsequent target vessel failure [59].

Collectively, these data indicate that intracoronary imaging enhances mechanistic understanding, procedural optimization, and long-term outcomes in ISR, supporting its use for a tailored, mechanism-driven revascularization approach [60, 61]. Accordingly, the value of intracoronary imaging for optimizing ISR treatment has been endorsed (IIa C recommendation) by the European Society of Cardiology clinical practice guidelines [41]. Nevertheless, it is important to acknowledge that currently no RCT exists comparing the real value of intracoronary imaging to guide interventions in patients with

ISR. Likewise, although intracoronary imaging is able to visualize and tackle the mechanical underlying issues frequently detected in patients with ISR, precise optimization criteria after DCB are lacking in this scenario. This highlights the importance of future studies in order to advance the field.

11.5.2 Lesion Preparation

Adequate mechanical lesion preparation is a critical step during DCB angioplasty in ISR to optimize acute lumen gain and ensure effective drug delivery. Restenotic tissue is often fibrotic or mechanically resistant, which may limit expansion with standard balloons and increase the risk of elastic recoil. In this setting, the use of plaque-modifying balloons, such as cutting and scoring balloons, creates controlled fracture lines within the plaque, enabling greater luminal expansion at lower inflation pressures and reducing the risk of acute elastic recoil, thereby potentially lowering the likelihood of recurrent ISR [62].

In addition to achieving optimal stent expansion, meticulous predilatation helps prevent balloon slippage outside the stent, the so-called "watermelon seeding" phenomenon, which may otherwise result in edge dissections. Moreover, inadequate coverage of injured stent edges by the DCB can subsequently lead to the characteristic "candy-wrapper" pattern of edge restenosis [60, 61].

The potential benefit of aggressive lesion preparation with special balloons has been specifically investigated in patients with ISR undergoing DCB angioplasty. In the ISAR-DESIRE 4 RCT, 252 patients with ISR after limus-DES implantation were randomized to conventional balloon predilatation or scoring balloon predilatation followed by DCB angioplasty. Scoring balloon predilatation resulted in significantly improved angiographic outcomes at follow-up. In particular, percent diameter stenosis, the primary endpoint, was lower in the scoring balloon group (35.0 ± 16.8% vs 40.4 ± 21.4%; $p = 0.047$), and the rate of binary restenosis was significantly reduced (18.5% vs 32.0%; $p = 0.026$) [63].

Complementary real-world data were provided by Linares et al., who evaluated lesion preparation strategies during DCB angioplasty in 91 patients with ISR, of whom 51 were treated with cutting balloons. Use of cutting balloons was associated with greater acute lumen gain and lower residual diameter stenosis compared with conventional balloon predilatation. At 5-year follow-up, cutting balloon use was associated with numerically lower rates of TLR compared with standard balloon predilatation (9.8% vs 23.6%; $p = 0.05$) [64].

The potential value of special balloons in "de novo lesions" is, however, less well established. At TCT 2025, a small RCT was presented comparing the use of cutting balloon vs conventional balloons before PCB treatment of de novo lesions. Although the use of cutting balloon was associated with some advantages, the results of the primary endpoint (achievement of adequate lesion preparation [including the following criteria: (1) no flow-limiting dissections, (2) residual stenosis ≤30% and (3) fractional flow reserve >0.80]) were similar in the two arms [65]. Again, this small trial further emphasizes the need for additional studies to understand how to improve the results of lesion preparation, in different clinical and anatomic scenarios, before DCB therapy.

11.6 Potential Treatment Algorithm for In-Stent Restenosis

We proposed an algorithmic approach for ISR that is organized in a few steps [4]. Firstly, identify the predominant mechanism of stent failure using intravascular imaging. Then, perform mechanism-specific lesion preparation to enhance the existing stent environment (referred to as "old stent improvement"). Finally, select the appropriate definitive antiproliferative therapy, whether that be DCB or DES (Fig. 11.5).

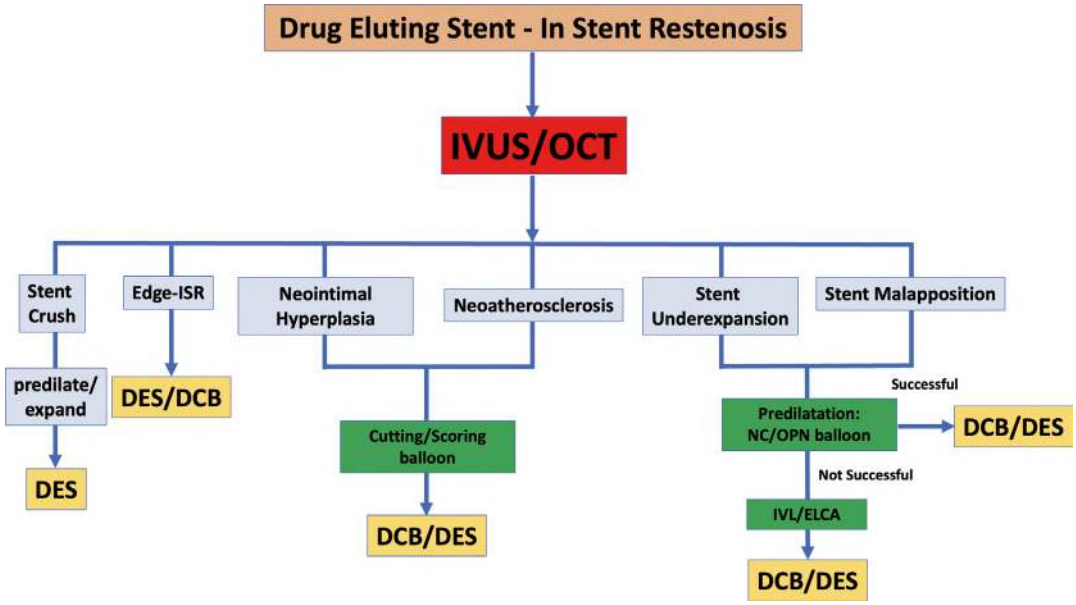


Fig. 11.5 Algorithmic approach to ISR. (From [4]). *Abbreviations*: DCB, drug-coated balloons; DES, drug-eluting stents; IVUS, intravascular ultrasound, NC, non-compliant; OCT, optical coherence tomography

11.6.1 Identification of the ISR Characteristics and Mechanism

Intracoronary imaging enables a more comprehensive ISR evaluation by allowing:

- Identification of both biological and mechanical contributors to ISR, which frequently coexist, particularly in high-risk patients with DM, CKD, complex coronary anatomy, or a history of restenosis (Fig. 11.6). In particular, identifying and tackling underexpansion remains crucial in the treatment of these patients.
- Detailed characterization of plaque morphology, the extent and severity of calcification, and the presence of neoatherosclerosis, which are poorly characterized by angiography alone [66].
- Quantitative assessment of minimal lumen area (ISR lesion severity) and stent expansion, parameters that have demonstrated prognostic relevance.

Taken together, these features support the use of intracoronary imaging over angiography alone for the evaluation and treatment of ISR [67, 68].

11.6.2 Lesion Preparation and Final Antiproliferative Therapy

In the ISR lesion, which contains neointimal hyperplasia, has good stent expansion, and has minimal calcium, it is recommended to use a non-compliant balloon followed by either cutting or scoring balloons. Subsequently, final DCB or DES should be considered.

An appealing concept is that in patients with ISR, the underlying tissue obstructing the stent may affect the relative efficacy of these alternative treatment modalities (DES vs DCB). Some studies suggested that in patients with ISR showing homogeneous tissue by OCT, both DES and DCB provide similar clinical results, whereas DES may be superior to DCB in patients with non-homogeneous tissue [69].

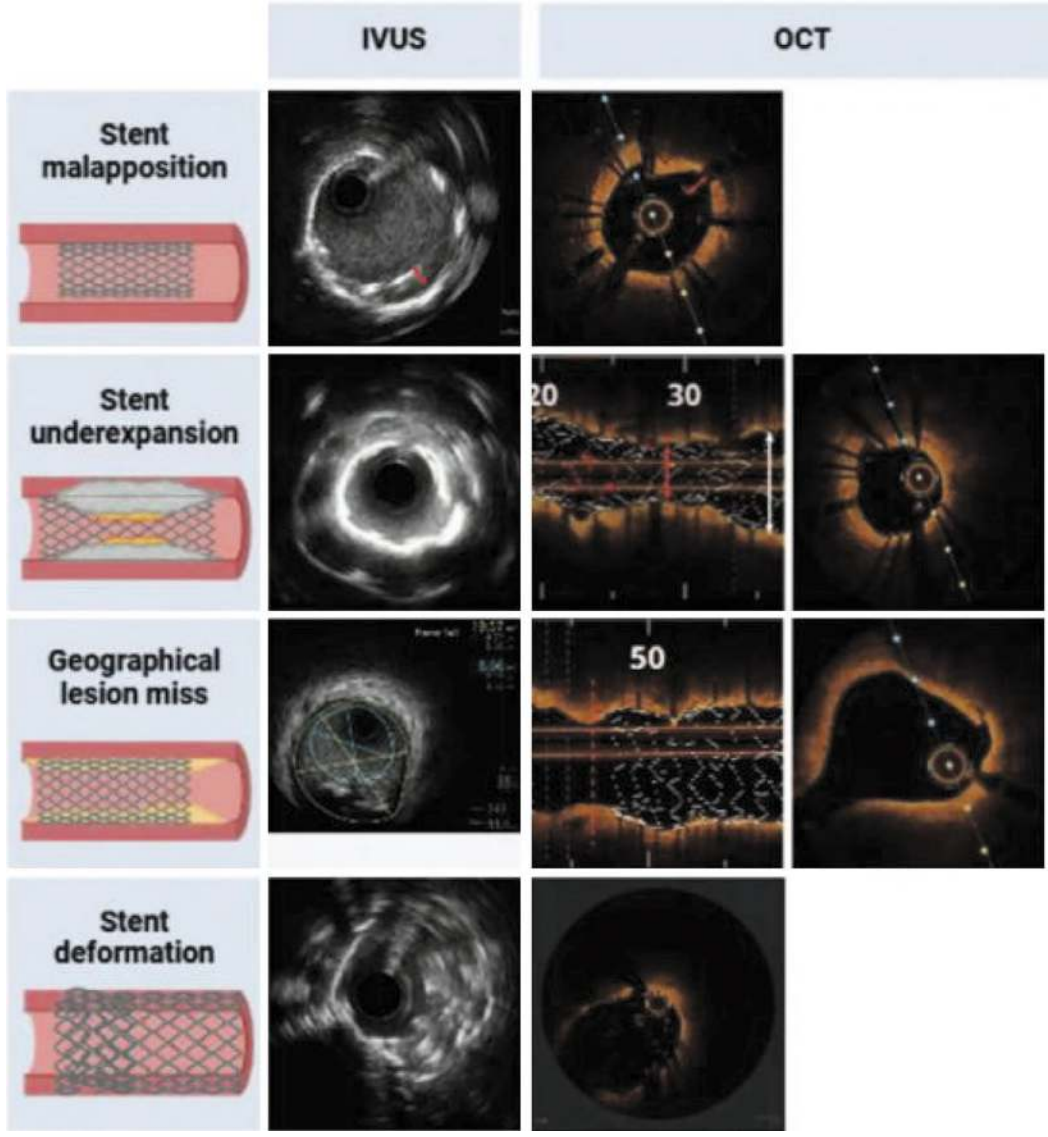


Fig. 11.6 Intracoronary imaging assessment of mechanical mechanisms of ISR. (From [4]). *Abbreviations*: IVUS, intravascular ultrasound, OCT, optical coherence tomography

To specifically address this question, the currently ongoing ISAR-DESIRE V RCT is allocating patients with ISR to either DES or DCB according to the type of tissue obstructing the stent as characterized by OCT (homogeneous vs non-homogeneous) [54].

For an ISR lesion caused by stent underexpansion or malposition due to external calcification, the initial approach involves appropriate predilatation using a high-pressure balloon, such as a non-compliant balloon or an OPN balloon. If this approach is insufficient, other treatment options for severe ISR with calcifications include rotational atherectomy, IVL, or excimer laser coronary atherectomy (ELCA).

Intravascular imaging, and OCT in particular, are of major value to visualize the calcific plates of calcified neoatherosclerosis within the stent.

This should be differentiated from a severely underexpanded stent due to a "napkin ring" calcification pattern outside the stent. Calcified neoatherosclerosis is detected in up to 13% of unselected patients with ISR and is associated with more demanding procedures and poorer acute results. The use of rotational atherectomy may be of value in highly selected cases, although nowadays IVL represents a readily available user-friendly device for these challenging cases [70–74].

The multicenter IVL-ELCA DRAGON Registry demonstrated that both IVL and ELCA achieved similar success and safety outcomes in treating resistant underexpanded stents [75]. Therefore, in centers experienced with ELCA treatment, this method may be applied to cases of in-stent calcified neoatherosclerosis or underexpanded stents when other interventions have failed.

The choice between DCB and DES should take into account the end of the procedure after adequate lesion preparation (≤20–30% residual stenosis, no major dissection), and involve re-evaluation using intravascular imaging. A suboptimal result despite meticulous predilatation will favor the use of DES, whereas a final DCB strategy is more appealing in patients obtaining an excellent result with predilatation. DES are recommended in patients with ISR as the result of stent fracture. In cases with resistant severe underexpansion of the target stent, implantation of another stent should be avoided although the results of DCB in this setting are also suboptimal. In patients with BMS-ISR, DCB should be preferred as in this scenario DES do not provide superior clinical outcomes. The presence of a relevant side-branch arising from the ISR lesions should favor the final use of DCB over DES to avoid double jailing of the branch. DCB are preferred by many operators in the first episode of ISR because DES may always be used later should recurrences occur. The number of stent layers, vessel size, and the clinical scenario (i.e., high bleeding risk) should all be considered in the decision-making process [76–78].

11.7 Conclusions

DCB represents a safe and effective strategy for the treatment of ISR, as they avoid the risks associated with additional stent layers, including late stent thrombosis, neoatherosclerosis, and malapposition. DCB may also offer an advantage when shortening dual antiplatelet therapy is desirable, particularly in patients at high bleeding risk. However, evidence comparing DES and DCB in ISR remains heterogeneous and largely derived from studies without routine intracoronary imaging. Future studies incorporating systematic intracoronary imaging are warranted to better define the role of DCB in ISR and optimize procedural results and long-term clinical outcomes.

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12 The Role of Drug-Coated Balloons for the Treatment of Small Native Coronary Vessels

Raban V. Jeger

12.1 Introduction

De-novo small-vessel coronary artery disease, often defined as de-novo lesions in arteries with reference diameters of <3.0 or <2.75 mm, remains a challenging scenario in interventional cardiology [1]. In these small vessels, even minor neointimal proliferation can translate into a substantial relative loss of lumen, impairing perfusion disproportionately compared to larger vessels. Stent implantation in such small arteries is complicated by the increased risk of restenosis, aggravated by the proportionally larger burden of struts in a limited lumen. Against this background, drug-coated balloons (DCB) have emerged as an attractive "leave-nothing-behind" strategy. By delivering an antiproliferative drug during brief balloon inflation yet avoiding permanent implantation, DCB offer a way to suppress neointimal growth without the long-term drawbacks of metallic scaffolds.

Mechanistically, DCB therapy in small coronary arteries depends on efficient drug uptake, retention, and biological effect, with minimal vessel trauma. Paclitaxel-coated balloons have long been the dominant technology because paclitaxel's lipophilicity allows rapid delivery during short inflation (typically 30–60 s) and durable tissue retention. More recently, sirolimus-coated balloons have been developed, using advanced formulations—such as crystalline matrices or micro-reservoirs—that sustain drug release and may offer improved pharmacokinetics in the thin-walled architecture of small vessels.

Over the past two decades, clinical evidence has grown from early single-arm studies to large, randomized trials and meta-analyses (Table 12.1). These data now inform a nuanced understanding of where and how DCB fit into the therapeutic armamentarium for small-vessel percutaneous coronary intervention (PCI).

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Table 12.1 Randomized controlled trials for DCB in de-novo small-vessel coronary disease

Trial name	Reference vessel size	Devices used	Follow-up duration	Key results
BELLO [4–6]	<2.8 mm	PCB (IN.PACT falcon) vs paclitaxel-eluting stent (taxus Liberté)	6 months 3 years	*6 months*: Lower LLL DCB vs. DES (0.08 vs 0.29 mm, $p = 0.001$) *3 years*: Lower MACE DCB vs. DES (14.4 vs. 30.4%, $p = 0.015$)
PICCOLETO II [8, 9]	2.0 mm –2.75 mm	PCB (Elutax SV) vs everolimus-eluting stent (Xience)	6 months 3 years	*6 months*: Lower LLL DCB vs. DES (0.04 mm vs 0.17 mm, p non-inferiority = 0.001; p superiority = 0.03) *3 years*: Lower rates MACE DCB vs. DES (10.8 vs. 20.8%, $p = 0.046$)
BASKET-SMALL 2 [10, 11]	≤ 2.75 mm	PCB (sequent please) vs drug-eluting stents (Xience, taxus element)	1 year 3 years	*1 year*: Non-inferiority MACE for DCB vs. DES (HR 0.97, 95% CI 0.58–1.64, $p = 0.9180$, p for non-inferiority = 0·0217) *3 years*: Similar rates MACE DCB vs. DES (HR 0.99, 95% CI 0.68–1.45; $p = 0.95$)
RESTORE SVD China [13, 14]	≥ 2.25 mm – ≤ 2.75 mm	PCB (RESTORE) vs zotarolimus-eluting stent (resolute integrity)	9 months 2 years	*9 months*: Non-inferiority % diameter stenosis DCB vs. DES (29.6% vs 24.1%, p non-inferiority <0.001) *2 years*: Similar rates target lesion failure (5.2% vs 3.7%, $p = 0.75$)

DCB drug-coated balloons, *DES* drug-eluting stent, *LLL* late lumen loss, *MACE* major adverse cardiac events, *PCB* paclitaxel-coated balloon

12.2 Biological and Mechanical Rationale in Small Vessels

The success of any interventional therapy depends in part on the interplay between vessel geometry, injury, healing, and drug pharmacology. In small coronary arteries, the structural and functional characteristics amplify certain challenges. The limited cross-sectional area of the vessel leads to the fact that any neointimal proliferation significantly reduces lumen size. After angioplasty, elastic recoil and dissection may cause greater relative compromise because small arteries have thinner walls and less capacity to absorb stress. The presence of a metallic stent in such a vessel often exacerbates these problems: the relative volume of the struts within the lumen is large, potentially causing flow disturbance, delayed endothelial healing, and inflammatory activation, which again may lead to restenosis.

By contrast, DCB therapy avoids these mechanical pitfalls. During inflation, the balloon delivers drug to the vessel wall without leaving behind a rigid structure. With no permanent implant, the artery retains its compliance, and vasomotion may be preserved. In addition, the absence of a stent reduces the chronic foreign-body stimulus that can promote neoatherosclerosis or late thrombosis. The key, then, lies in achieving an acceptable result after lesion preparation as outlined in International DCB Consensus Groups and ARC [2–4], and also in an efficient, durable drug delivery into the vessel wall—a task that modern DCB technology is increasingly capable of performing.

12.3 Clinical Evidence from Early to Recent Trials

12.3.1 Early Experience: PEPCAD I

The PEPCAD I study was one of the first prospective evaluations of DCB therapy in de-novo small-vessel coronary artery disease. This single-arm trial enrolled 120 patients with vessels mea-

suring 2.25–2.8 mm and treated them primarily with a crystalline paclitaxel-iopromide coated balloon [5]. At the 36-month follow-up, major adverse cardiac events (MACE) were only 6.1% in patients treated with a DCB-only strategy, establishing long-term efficacy and safety and setting the foundation for future randomized trials [6].

12.3.2 BELLO Trial

The BELLO trial was a multicenter randomized study evaluating a crystalline paclitaxel-coated balloon versus a paclitaxel-eluting stent in 182 patients with small coronary arteries (<2.8 mm) [7]. The primary endpoint, in-lesion late lumen loss at 6 months, favored the DCB group (0.08 ± 0.38 mm) compared to the stent group (0.29 ± 0.44 mm, p for noninferiority < 0.001, p for superiority = 0.001). Rates of restenosis, target lesion revascularization, and MACE were similar at 6 months, with a trend toward lower 2-year MACE in the DCB arm [8]. This difference became significant after 3 years, with lower rates of MACE in the DCB as compared with the drug-eluting stent (DES) group (14.4 vs. 30.4%, $p = 0.015$) [9]. Subgroup analyses demonstrated specific benefits in diabetic patients, highlighting the effectiveness of DCB therapy in this important subgroup [10].

12.3.3 PICCOLETO II Trial

The PICCOLETO II trial enrolled 232 patients with vessels measuring 2.0–2.75 mm and randomized them to an amorphous paclitaxel-coated balloon or an everolimus-eluting stent [11]. At 6 months, in-lesion late lumen loss was significantly lower in the DCB (0.04 ± 0.21 mm) vs. the DES group (0.17 ± 0.25 mm; p for superiority = 0.03). Clinical outcomes at 12 months were comparable, while the 3-year follow-up demonstrated lower cumulative MACE in the DCB group (10.8% vs 20.8%; $p = 0.046$) with no acute vessel thrombosis, supporting both safety and durability [12].

12.3.4 Pivotal Evidence: The BASKET-SMALL 2 Trial

The BASKET-SMALL 2 randomized trial marked a turning point in DCB research. A total of 758 patients with de-novo lesions in vessels <3 mm were randomized after successful predilatation to either crystalline paclitaxel DCB angioplasty or second-generation DES implantation. The trial demonstrated that DCB therapy was non-inferior to DES at 12 months for the composite endpoint of cardiac death, nonfatal myocardial infarction, and target-vessel revascularization [13]. Long-term follow-up reinforced these findings, with sustained similarity in clinical outcomes over 36 months [14]. In the diabetic subgroup, the rates of target-vessel revascularization were significantly lower with DCB versus DES, demonstrating the sustained efficacy and safety of DCB in diabetic patients with de-novo lesions of small coronary vessels up to 3 years [15].

12.3.5 RESTORE SVD China Trial

The RESTORE SVD China trial provided further randomized evidence in small-vessel disease using a different DCB platform. In this multicenter study, 230 patients with reference vessel diameter 2.25–2.75 mm were randomized 1:1 to another amorphous paclitaxel-coated DCB or a zotarolimus-eluting stent [16]. In a nested registry, 32 additional patients with very small vessels with a diameter 2.00–2.25 mm were treated with the DCB. At 9 months, the primary angiographic endpoint—in-segment diameter stenosis—demonstrated non-inferiority of the DCB versus DES (29.6 ± 2.0 vs. 24.1 ± 2.0%; p-non-inferiority <0.001). At 1 year, rates of target lesion failure, defined as a composite of cardiac death, myocardial infarction, and target-vessel revascularization, were similar between the therapies (4.4% vs. 2.6%, $p = 0.72$). Two-year follow-up confirmed that there was no significant difference in target lesion failure (5.2% vs. 3.7%, $p = 0.75$), supporting the longer-term safety of the DCB strategy [17]. In a functional substudy, quantita-

tive flow ratio at 9 months was similar between DCB and DES arms, reinforcing the physiological equivalence of the two strategies in small vessels [18].

12.3.6 Pooled Evidence: The ANDROMEDA Meta-Analysis

The ANDROMEDA meta-analysis represents a landmark pooled patient-level study that synthesizes data from multiple small-vessel DCB trials. Investigators collected individual patient data of 1154 patients from key randomized trials including BELLO, BASKET-SMALL 2, and PICCOLETO II, and reconstructed patient-level time-to-event data for the RESTORE SVD China trial to perform a comprehensive analysis [19]. In repeated one-stage and two-stage models, the study examined long-term outcomes up to 3 years. The primary endpoint MACE, defined as all-cause death, myocardial infarction, target lesion revascularization, and lesion thrombosis, was significantly lower in the DCB-treated group in the one-stage model (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.47–0.96; $p = 0.027$). After adjustment for covariates, the benefit persisted (adjusted HR 0.75; 95% CI 0.58–0.96). The reduction in risk was driven mainly by fewer myocardial infarctions (4.7 vs. 7.8%) and lower target-vessel revascularization (11.1 vs. 15.6%). However, the co-primary lesion-based endpoint, target lesion failure, was not statistically different between DCB and DES arms in the sensitivity analyses (HR 0.87; 95% CI 0.63–1.20). These findings highlight that, on a patient level, DCB therapy in small coronary vessels may confer significant long-term advantages, especially in reducing MACE, and suggest that the "leave-nothing-behind" strategy may yield meaningful clinical benefits over prolonged follow-up. The ANDROMEDA analysis underscores the importance of DCB therapy beyond lesion-level surrogate endpoints and supports its use as a foundational therapy in small-vessel disease.

12.3.7 The REC-CAGEFREE I Trial

In the REC-CAGEFREE I trial, 2272 patients with de-novo, non-complex coronary lesions, independent of vessel size, were randomized after successful predilatation to either a crystalline paclitaxel-coated balloon angioplasty with rescue (bailout) stenting or intended second-generation thin-strut sirolimus-eluting stent implantation [20]. At 3 years follow-up, the device-oriented composite endpoint (cardiovascular death, target-vessel myocardial infarction, and clinically or physiologically indicated target lesion revascularization) occurred in 8.2% of the DCB arm compared to 5.0% of the DES arm, thus failing to meet the non-inferiority criteria. Subgroup analyses revealed that in smaller vessels (device diameter <3.0 mm), outcomes were comparable between DCB and DES, whereas in larger vessels, DCB was clearly less effective, indicating a size-dependent therapeutic window. Limitations of this study include a potentially inaccurate lesion preparation (given the high bailout stent rate of 9%), the unknown efficacy of the DCB used, the open-label design, and the fact that only non-complex lesions were included [21, 22].

12.4 Lumen Gain and Positive Remodeling in Small-Vessel Disease

In small coronary vessels, the concept of late lumen gain—an increase in luminal diameter over time after the procedure—has been most convincingly documented with paclitaxel-coated balloons. Evidence comes from two studies. In the first study, 58 de-novo native coronary lesions treated with a DCB-only strategy were followed angiographically over approximately 4 months [23]. Quantitative coronary angiography showed a significant increase in the minimal lumen diameter from immediately post-procedure to follow-up (from about 1.75 to 1.91 mm, $p < 0.001$), even though the reference vessel diameter remained unchanged. In this cohort, 69% of lesions demonstrated lumen enlargement, suggesting a true pos-

itive remodeling effect induced by local paclitaxel delivery. In another study in native coronary lesions left with residual dissections after balloon angioplasty, DCB treatment was associated with progressive vessel recovery rather than adverse remodeling [24]. Mechanistic hypotheses supported by these observations suggest that paclitaxel's local effects go beyond simply suppressing neointimal hyperplasia. Rather, the drug may modulate the extracellular matrix, dampen inflammation, and permit Glagov-type remodeling, where the vessel wall expands outward to preserve or even increase lumen size [25].

12.5 Diabetes Mellitus

Diabetes mellitus represents a high-risk patient group in the context of small-vessel coronary artery disease, not only because of the higher prevalence of diffuse, calcific, and long lesions in diabetic patients, but also due to the more aggressive vascular biology associated with hyperglycaemia. Under diabetic conditions, endothelial dysfunction, chronic inflammation, and proliferative responses to injury are accentuated, leading to increased neointimal hyperplasia and late lumen loss after PCI. In small vessels, these biological disadvantages are magnified: even modest neointimal growth or late constriction translates into proportionally greater luminal compromise, and technical issues such as stent under-expansion or incomplete apposition are more frequent in diabetics, increasing the risk of restenosis, stent thrombosis, or the need for repeat revascularization. The BASKET-SMALL 2 trial provided prespecified subgroup analyses by diabetes status. Over a 3-year follow-up involving 252 diabetic patients (out of 758 total), rates of MACE did not differ significantly between DCB and DES arms (19.3 vs. 22.2%; HR 0.82, 95% CI 0.45–1.48; p = 0.51). Remarkably, the need for target-vessel revascularization was significantly lower in the diabetic DCB group (9.1 vs. 15.0%; HR 0.40, 95% CI 0.17–0.94; interaction p = 0.011), suggesting a particular benefit in reducing repeat interventions in this high-risk cohort [15]. Further scrutiny within BASKET-SMALL 2 distinguished between insulin-treated (ITDM) and non–insulin-treated (NITDM) diabetes. Among the 157 NITDM patients, MACE rates were numerically lower with DCB (16.7 vs. 21.9%; HR 0.68, 95% CI 0.29–1.58), and there was a strong trend toward reduced target-vessel revascularization (8.4 vs. 14.5%; HR 0.30, 95% CI 0.09–1.03; p = 0.057). In the 95 ITDM patients, outcomes were broadly comparable between DCB and DES (MACE 23.4 vs. 22.7%, HR 1.12, 95% CI 0.46–2.74; target-vessel revascularization 10.1 vs. 15.7%, HR 0.64, 95% CI 0.18–2.27). Across all diabetics, the DCB strategy yielded a statistically significant 59% reduction in target-vessel revascularization (HR 0.41, 95% CI 0.18–0.95; p = 0.038) [26]. Older, smaller randomized data from the BELLO trial also support the concept that diabetes does not negate the angiographic and clinical advantages of DCB in small vessels. In a subanalysis of 74 diabetic patients (DCB n = 39; paclitaxel-eluting stent n = 35), late lumen loss at 6 months was markedly lower with the drug-eluting balloon than with the stent (0.05 ± 0.41 mm vs. 0.30 ± 0.51 mm; p = 0.033), and binary restenosis rates in-segment were significantly reduced (6.3 vs. 25.0%; p = 0.039), with similar 1-year major adverse event rates in both arms [10]. Beyond single trials, a recent meta-analysis that pooled data from ten studies (totaling 2026 diabetic patients with small-vessel disease) found that at a mean follow-up of 15.3 months, DCB were associated with significantly lower mortality (3.2% vs. 4.9% with DES; OR [95% CI] = 0.61 [0.38, 0.97], p = 0.04). Similarly, MACE also resulted lower with DCB (13.6% vs. 17.6%; OR [95% CI] = 0.79 [0.61, 1.04], p = 0.09) [27]. Taken together, these data underscore that diabetes, while a major risk amplifier in small-vessel coronary disease, does not appear to blunt the relative efficacy of DCB strategies. On the contrary, diabetic patients treated with DCB may derive particular benefit—especially in terms of reduced repeat revascularization—thereby supporting the use of a "leave-nothing-behind" approach in this challenging population.

More recently, sirolimus was also developed and studied as a drug carried and delivered by

DCB. The FASICO NATIVES study was the first prospective registry to test its safety and efficacy in SVD, showing a LLL of 0.09 ± 0.34 mm in 27 consecutive patients enrolled and analyzed by an independent core laboratory [28]. The prospective, investigator-driven EASTBOURNE study showed a good clinical performance of this nanocarrier sirolimus DCB with TLR occurring in 2% and 3% at 1 and 2 years follow-up in the SVD setting [29, 30].

12.6 Clinical Implications and Procedural Considerations

Given this scientific evidence, an approach of leaving nothing-behind using DCB therapy for de-novo small-vessel disease shows good results with high safety standards, and represents current practice in many countries, though it has not been recognized by current guidelines. Of utmost importance, procedural technique is essential. Adequate lesion preparation—with predilatation aimed to achieve acceptable results (no flow-limiting dissection, maximum 30–40% residual stenosis)—is a prerequisite. Oversizing or undersizing the balloon relative to vessel diameter can impair drug delivery or provoke injury. Operators should favor sufficiently long inflation times to maximize drug uptake. Although "bailout" stenting may remain part of the strategy, the goal is to minimize permanent implant whenever feasible. Positive remodeling of the vessel may contribute to beneficial long-term results [3, 4].

12.7 Future Directions and Research Needs

While the current evidence strongly supports DCB use in small-vessel PCI, several areas warrant further investigation. Larger, dedicated randomized trials of sirolimus-coated balloons in small-vessel de-novo disease are needed to establish their long-term efficacy and safety, and the results of TRANSFORM II RCT are awaited in 2026 [31]. Further, intravascular imaging–guided strategies may optimize lesion preparation and reduce the need for bailout stenting, particularly in small and tortuous arteries. Long-term follow-up beyond 2–3 years would clarify whether trends in clinical outcome observed in meta-analyses persist, diminish, or worsen with time as compared to the current gold standard with stents. Finally, real-world registries capturing contemporary device iterations, diverse patient populations, and operator experience will be invaluable in defining best practices.

12.8 Conclusion

Drug-coated balloons represent a highly attractive intervention for small native coronary arteries, combining effective antiproliferative therapy with a leave-nothing-behind philosophy. The clinical trial data, including randomized studies and meta-analyses, overwhelmingly support their use in de-novo small-vessel disease. Recent innovations such as sirolimus-coated balloons may expand the therapeutic toolbox and promise to refine outcomes further. With careful procedural technique, patient selection, and ongoing research, DCB are poised to become a central modality in the management of small-vessel coronary artery disease.

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13 The Role of Drug-Coated Balloons in Complex Coronary Artery Disease: Chronic Total Occlusions

Evandro Martins Filho and Bernardo Cortese

13.1 Introduction

Drug-coated balloons (DCB) have emerged as an important advancement in percutaneous coronary interventions (PCI). Originally developed for the treatment of in-stent restenosis (ISR), their applications have expanded to include small-vessel disease (SVD), bifurcation lesions, and increasingly complex coronary anatomies such as long lesions and chronic total occlusions (CTO) [1, 2].

Unlike drug-eluting stents (DES), DCB deliver antiproliferative agents without leaving behind a permanent metallic scaffold. This "stent-free, no-permanent-implant" approach is particularly advantageous in settings where stent implantation is associated with long-term risks, including restenosis, thrombosis, neoatherosclerosis, and adverse vessel remodeling [2, 3].

This chapter explores the rationale, clinical evidence, procedural considerations, and future perspectives on the use of DCB in CTO PCI and other complex coronary disease scenarios.

13.2 Rationale for DCB Use in Complex CAD and CTO

In the treatment of complex coronary artery disease (CAD), especially CTO, DCB offer several theoretical and practical advantages. Long stented segments are known to increase the risk of late complications, such as: (1) In-stent restenosis, (2) Late thrombosis, (3) Neoatherosclerosis, and (4) Loss of vasomotion [3, 4].

In this lesion setting PCI frequently requires multiple overlapping stents due to lesion length, tortuous anatomy, and diffuse disease. Reducing stent length and number through an alternative approach like DCB may significantly mitigate these complications.

Additionally, DCB therapy has been associated with late lumen enlargement (LLE), a phenomenon opposite to the chronic lumen loss seen with DES [5]. This biological profile supports the use of DCB in long and complex lesions where long-term healing and vascular physiology are critical to clinical success.

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13.3 Current Clinical Evidence

A growing body of clinical evidence supports the role of DCB in PCI for CTO and complex coronary lesions:

- A meta-analysis involving over 14,000 CTO patients demonstrated that successful CTO PCI, regardless of device, improves mortality and symptom relief. When DCB are incorporated into these strategies, registry data suggest lower MACE during follow-up [3].
- Shin et al. observed that a DCB-based strategy led to shorter stent length and fewer adverse events at two-year follow-up compared to DES-only approaches [6].
- Yan et al. found that in patients with CTO and distal diffuse disease, a DES + DCB hybrid approach reduced MACE and cardiovascular hospitalization compared to DES alone [4].
- Zhao et al., in a 2024 meta-analysis, reported a 13% MACE rate in DCB-treated CTO, indicating acceptable safety and efficacy profiles [5].
- Observational registry data suggest that DCB may serve as a stent-free strategy in de novo CTO when adequate lesion preparation is achieved [7–9].
- The Natarajan et al. (2025) meta-analysis (n = 1695) showed consistent late lumen enlargement (LLE) and comparable outcomes between DCB, DES, and hybrid strategies [8].
- The European Registry of Chronic Total Occlusion (ERCTO) involving 40,449 cases noted increased use of DCB (from 3.4% in 2016 to 15% in 2023), with favorable outcomes including lower total stent length, reduced contrast usage, and decreased incidence of pericardial tamponade [9].
- The recently presented preliminary results of PICCOLETO X registry showed the safety and efficacy of a DCB approach (alone or in combination with DES) in CTO lesions (B. Cortese, LBCS @ TCT Conference, San Francisco, 2025). The study has now been published: in 938 patients treated at 21 international centers, 12-month target vessel failure was 9.5%, with no difference between DCB-only and blended DCB + DES strategies [20].
- A recently published meta-analysis is showing the safety and efficacy of a DCB approach vs a DES one in CTO lesions (2087 patients). The DCB-based group showed a trend towards a lower rate of TVF (0.45% (112/25045) vs. 0.76% (238/31336) person-months, IRR = 0.56 [95% CI 0.28 to 1.10], I2 = 81%, p = 0.09) and cardiac death (0.05% vs. 0.10% person-months, IRR = 0.55 [95% CI 0.27 to 1.10], I2 = 0%, p = 0.09) [10].

13.4 Favorable Clinical Scenarios

Drug-coated balloons provide unique advantages in several settings of complex coronary artery disease, particularly within CTO PCI**,** where long stented segments and heterogeneous vessel remodeling often increase the risk of adverse events.

By reducing the overall metallic footprint, DCB-based approaches can mitigate complications such as restenosis, stent thrombosis, and neoatherosclerosis, issues that are especially frequent in long or diffusely diseased CTO.

Key applications include:

- Reduction of total stent burden and metallic implant volume, especially after successful CTO recanalization involving long diffuse segments.
- Treatment of distal or diffusely diseased vessels beyond safe stenting zones, frequently observed in CTO where distal runoff is small or tapered.
- Management of small-vessel disease in the distal bed post-recanalization, where stent implantation may not be technically feasible or physiologically desirable.
- Treatment of side branches in bifurcation CTO, allowing therapy of jailed or re-entry segments without complex two-stent techniques.

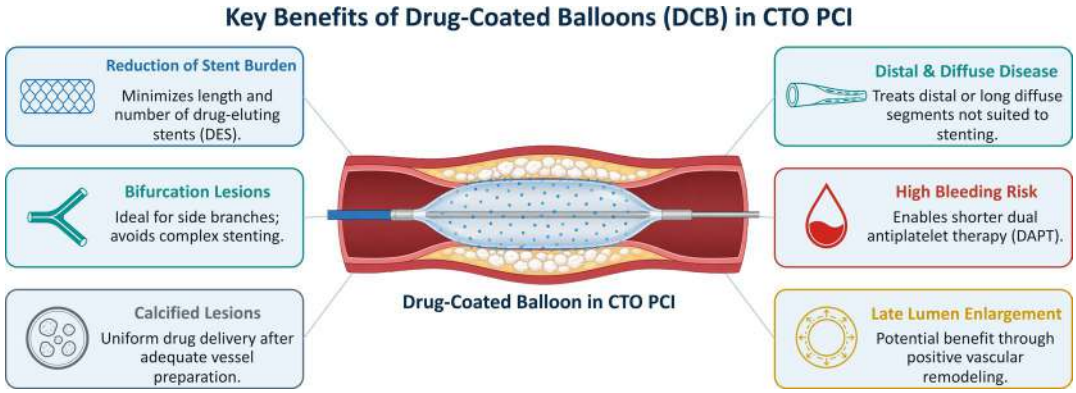


Fig. 13.1 Conceptual framework of the "leave-nothing-behind" strategy using drug-coated balloons, highlighting drug delivery without permanent metallic scaffolding and its potential advantages over drug-eluting stents in complex coronary lesions

- High bleeding risk patients, enabling shorter dual antiplatelet therapy (DAPT) regimens after extensive CTO PCI. [3, 11].
- Heavily calcified or fibrotic lesions, in which suboptimal stent expansion or malapposition could jeopardize outcomes.
- Lesions demonstrating late lumen enlargement (LLE) after DCB angioplasty, reflecting favorable healing and positive remodeling following recanalization. [4].

In the CTO setting, these advantages translate into a hybrid, physiology-oriented strategy combining DES in proximal anchor zones with DCB in distal or small-caliber segments achieving complete revascularization while minimizing long-term metallic burden (Fig. 13.1).

13.4.1 Myocardial Bridge-Related CTO and DCB Therapy

Myocardial bridging (MB) is a frequent anatomical variant, observed in 5%–30% of the general population and in up to 40% when assessed by intravascular imaging, most commonly involving the mid/distal left anterior descending (LAD) artery. In patients undergoing PCI for CTO, MB is identified in approximately 40% of LAD CTO, compared with about 25% of non-occlusive LAD lesions [12]. Although often benign, MB may coexist with proximal atherosclerotic plaque formation and contribute to dynamic systolic compression or re-occlusion within the tunneled segment, particularly after stent implantation.

CTO involving or adjacent to a myocardial bridge represents a particularly challenging subset due to the combination of fixed atherosclerotic obstruction proximally and dynamic compression distally. Stent implantation in this region has been associated with high rates of restenosis, stent fracture, and late thrombosis, owing to persistent mechanical stress and altered shear forces within the bridged segment.

Recent evidence suggests that a DCB-only strategy, guided by intravascular imaging, may offer physiological and procedural advantages in these anatomies. In a 12-month comparative study of 231 patients with proximal LAD stenosis and distal myocardial bridge, DCB angioplasty achieved lower late lumen loss (-0.04 ± 0.04 mm vs 0.18 ± 0.05 mm) and fewer major adverse cardiovascular events (9.6% vs 21.6%) than DES, while preserving vessel compliance and enabling shorter DAPT [13].

These findings align with previous case-based evidence [14] demonstrating complete one-year vessel patency after IVUS-guided DCB angioplasty of a mid-LAD bridge lesion, confirming the safety of a "leave-nothing-behind" approach. Thus, when CTO or severe stenosis occurs near a myocardial bridge, imag-

ing-guided DCB therapy, following meticulous lesion preparation, can restore patency while avoiding the structural and hemodynamic complications typical of stent placement within bridged segments.

13.5 Challenging Scenarios and Limitations

Despite the growing evidence supporting DCB therapy, several anatomical and procedural challenges may limit its universal application in CTO PCI [3, 11]:

- Flow-limiting dissections after extensive lesion preparation or subintimal tracking often necessitate bailout stenting, precluding a pure DCB strategy.
- Residual stenosis >30% following predilation or plaque modification significantly compromises drug transfer and long-term patency.
- Vessel recoil, particularly in large or heavily remodeled CTO segments, can offset the benefits of DCB angioplasty unless adequate debulking or scaffolding is achieved.
- Severe calcification or tortuous anatomy may impair balloon deliverability, reducing procedural efficiency and drug penetration.
- Dissection/re-entry techniques (ADR or RDR), while essential for some CTO revascularization, create non-intimal planes potentially at risk for DCB-only treatment and are better managed with hybrid DES + DCB approaches. In these cases, we could expect a higher drug uptake, which could potentially lead to an increase in the risk of developing coronary ectasia or aneurysms, especially with paclitaxel.
- Finally, operator experience and the absence of intravascular imaging remain critical determinants of success, influencing lesion preparation quality and the decision to pursue a stent-free result.

These anatomical and procedural limitations should be carefully assessed when planning a DCB strategy. Figure 13.2 summarizes favorable

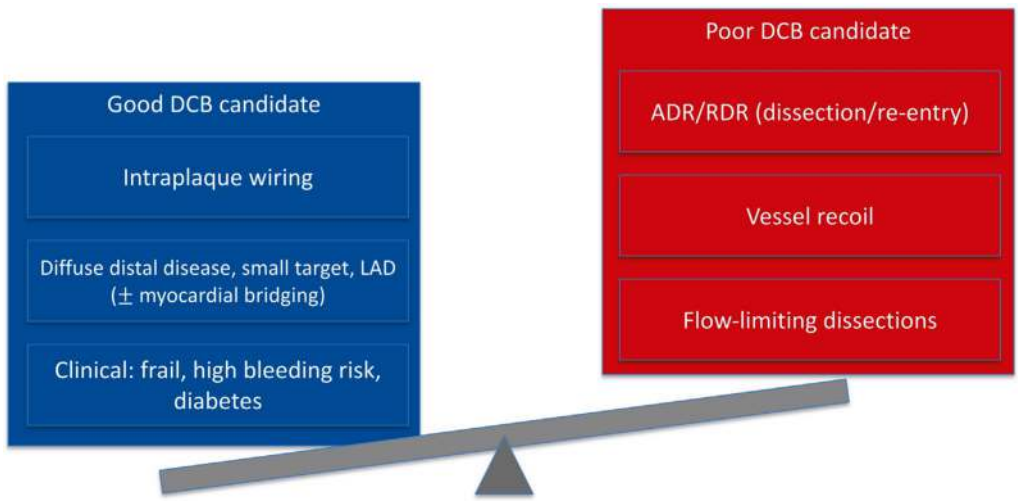


Fig. 13.2 Clinical and procedural factors influencing DCB feasibility in CTO PCI. Favorable conditions for a drug-coated balloon (DCB) strategy include intraplaque wiring, distal diffuse disease (particularly in small targets such as the LAD or within myocardial bridging), and clinical profiles with high bleeding risk or frailty. Conversely, DCB use is less suitable after antegrade or retrograde dissection/re-entry (ADR/RDR), in cases of significant vessel recoil, or flow-limiting dissections, where bailout stenting is often required

and unfavorable conditions influencing DCB feasibility in CTO PCI.

13.6 Technical Considerations in CTO PCI with DCB

Successful implementation of DCB therapy in CTO PCI requires meticulous lesion preparation and procedural planning (please see the relevant chapter of this book). The goal is to achieve optimal luminal expansion and vessel healing while minimizing the amount of permanent metal implanted.

Lesion Preparation
Like for other lesions setting, adequate predilation is crucial to create a smooth lumen and achieve ≤30% residual stenosis with TIMI 3 flow before DCB delivery. In the presence of heavy calcification or vessel recoil after initial predilatation with normal balloons, scoring or cutting balloons, rotational or orbital atherectomy (RA/OA), or intravascular lithotripsy (IVL) should be used to optimize expansion and minimize dissection. Also for CTO, proper preparation remains the single most important predictor of durable DCB success.

Intravascular Imaging
IVUS or OCT is recommended to confirm intraplaque wiring, assess vessel diameter and calcium burden, and guide balloon sizing and selection. Imaging helps anticipate elastic recoil, identify dissections, and recognize cases that would benefit from a hybrid DES-plus-DCB approach.

DCB Use in Subintimal Space
The use of DCB within subintimal or re-entry planes remains controversial and biologically uncertain. Because drug absorption relies on contact with a viable endothelial surface and intact microvasculature, drug transfer in subintimal tissue may be incomplete or inconsistent.

Although isolated reports [15] have described subintimal DCB angioplasty as a bailout strategy when true-lumen re-entry is not achievable, no consistent clinical evidence supports durable patency or vessel healing in this setting [11]. Consequently, blended revascularization, with DES at the re-entry site and DCB in true-lumen or distal segments, is generally preferred to maintain both mechanical integrity and biological benefit [11, 15].

13.6.1 Hybrid Revascularization Strategy

In many CTO, combining DES in proximal segments with DCB in distal or small-caliber vessels achieves complete revascularization while limiting total stent length. This hybrid concept merges mechanical support where needed with the biological advantages of a "leave-nothing-behind" approach [8].

13.6.2 DCB ARC 2025 Practical Standards

The 2025 Academic Research Consortium (ARC) position statement [11, 16] provides unified technical recommendations for DCB use in complex PCI, including CTO. DCB ARC gathered the most experts on this technology worldwide and gave the following suggestions to optimize the performance of DCB angioplasty:

- *Balloon-to-vessel ratio*: 1:1 (based on distal reference diameter)
- *Inflation time*: ≥30 s for lesion preparation, ≥60 s for DCB inflation (if tolerated)
- *Residual stenosis*: ≤30% with TIMI 3 flow prior to DCB use, or <40% focal in case of diffuse disease
- *Acceptable dissections*: Non-flow-limiting (TIMI 3, no ischemic signs)
- *DCB delivery time*: < 2 min after exposure to minimize drug loss
- *Imaging guidance*: IVUS/OCT for sizing and calcium assessment
- *CTO intraplaque wiring*: A DCB-only strategy can be achieved

- *Dissection–re-entry cases*: Hybrid DES + DCB approach, limiting DES to those segments where there is no certainty of being in the true vessel lumen

The DCB ARC highlights that there is no class effect among DCB, their performance depending on the specific drug, excipient, and coating technology. When these procedural standards are met, reported outcomes show restenosis/re-occlusion rates around 7%–8% and positive vessel remodeling in 50%–60% of cases at 1 year.

Special Clinical Subsets In high-bleeding-risk patients, as well as in diabetic or multivessel disease, DCB-based revascularization allows shorter DAPT regimens and reduces late stent-related events, further supporting its integration into contemporary CTO PCI practice.

13.6.3 DCB for Plaque Modification and Investment Procedures in CTO

Beyond conventional lesion preparation, DCB may play an emerging role in *plaque modification* and *investment procedures* following failed or suboptimal CTO recanalization. These techniques, which intentionally dilate the subintimal space to promote controlled healing and maintain a decent distal flow, have traditionally employed semi- or non-compliant balloons. Recent reports suggest that substituting the conventional device with a DCB can enhance local vessel biology by delivering antiproliferative agents to the dissection planes, thereby reducing tissue proliferation and improving vessel healing before a staged attempt.

In a pioneering series by Ybarra et al. [15], three cases of failed CTO PCI underwent subintimal plaque modification using paclitaxel DCB instead of conventional balloons. Follow-up angiography demonstrated partial resolution of dissection planes, maintenance of TIMI 3 flow, and improved wiring success during the staged reintervention. This approach, termed *DCB plaque modification*, was safe and feasible, suggesting potential benefits in preserving vessel patency and facilitating subsequent re-entry or distal wiring.

These findings were later integrated into the broader conceptual framework proposed by Sánchez-Jiménez et al. [17], who illustrated that DCB use after initial plaque modification may decrease neointimal proliferation and favor positive remodeling over time. The authors emphasized that this strategy could act as a biological bridge between an initial "investment" procedure and definitive revascularization, minimizing the need for extensive stenting and promoting natural lumen recovery.

In this context, DCB-mediated plaque modification may represent a valuable adjunct in CTO cases where complete revascularization cannot be achieved during the first attempt, particularly when antegrade or retrograde dissection/re-entry is used. Although current data remain limited to small series and case reports, this technique aligns with the *leave-nothing-behind* philosophy and supports the incremental use of DCB as tools not only for treatment but also for vessel conditioning and healing in complex CTO anatomy. Moreover, sparing inappropriate stent implantation in this setting may overcome some of the long-term limitations of prostheses, including acquired late malapposition or inappropriate vessel sizing. Prospective studies are warranted to better define optimal timing, drug formulations, and clinical outcomes of this approach.

Emerging evidence suggests that sirolimus-coated balloons, due to their more sustained antiproliferative effect and reduced toxicity in hypoxic environments [18], may further enhance the biological potential of DCB-assisted plaque modification. These properties could expand the applicability of this strategy to more complex CTO anatomies and staged revascularization plans.

13.7 Future Perspectives

The expanding development of sirolimus-based DCB technologies and novel crystalline, amorphous, or micro-reservoir coating platforms is

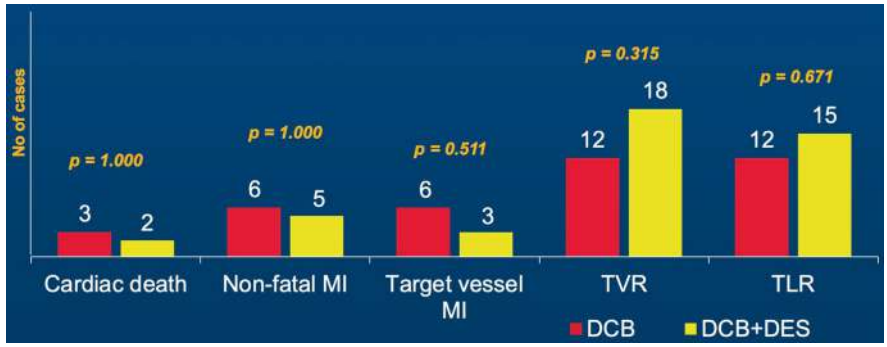


Fig. 13.3 Preliminary 12-month clinical results of PICCOLETO X study, a multicenter, multinational study on the clinical performance of DCB (alone or in a blended fashion with DES) in CTO. This figure shows the absence of clinical difference between these 2 strategies in CTO revascularization. (B. Cortese, LBCS@TCT Conference, San Francisco, 2025)

broadening the therapeutic scope of DCB use in complex coronary disease.

Future developments and ongoing studies are expected to further define and expand the role of this strategy, particularly in CTO PCI:

- The Co-CTO trial (NCT04881812) is the first randomized controlled study designed to compare a hybrid DES + DCB strategy with a complete stenting approach in patients undergoing CTO PCI, aiming to determine whether a reduced-metal approach can achieve comparable luminal and clinical outcomes [19].
- Longer-term follow-up of the multicenter, international PICCOLETO X study (Chairman: B. Cortese), whose 12-month results in 938 patients have now been published [20], will further define the durability of solo-DCB and blended DCB-DES strategies in CTO PCI (see Sect. 13.3).
- Next-generation sirolimus-coated DCB may provide more consistent drug delivery and improved endothelial healing compared with traditional paclitaxel-based platforms [18].
- The integration of physiological guidance (FFR/iFR or μQFR), computational vessel modeling, and artificial intelligence (AI) promises to enhance case selection and procedural optimization [17].
- Further investigation is needed to refine lesion preparation protocols and define the optimal use of DCB-only strategies in real-world CTO interventions. In particular, a deeper understanding of the biological behavior and clinical outcomes of DCB application within subintimal spaces is required, as current evidence on drug transfer and vessel healing in these planes remains limited [19] (Fig. 13.3).

13.8 Conclusions

DCB have emerged as a viable and increasingly utilized option for the treatment of complex coronary artery disease, particularly in long lesions and CTO. They reduce the need for extensive stenting, promote late lumen enlargement, and offer favorable outcomes in scenarios such as small vessels, distal disease, bifurcations, and high bleeding risk. Although challenges like dissections and residual stenosis remain, accumulating evidence supports the safe and effective use of DCB in selected cases. Ongoing randomized trials will be essential in solidifying the role of DCB in routine CTO PCI practice. As technology and technique converge, DCB therapy in CTO PCI embodies the modern paradigm of minimalistic yet durable coronary intervention.

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14 The Role of Drug-Coated Balloons for Complex Coronary Artery Disease: Bifurcations

Tuomas T. Rissanen

14.1 Rationale for DCB in Coronary Bifurcations

A coronary bifurcation lesion (CBL) is a coronary artery lesion that involves a significant side branch (SB). CBL is a significant challenge as up to 20% of percutaneous coronary intervention (PCI) procedures involve a bifurcation lesion [1]. Interventions on CBL are technically challenging and are associated with higher complication and restenosis rates compared to lesions that do not involve a bifurcation [2]. The restenosis rates are particularly high in an SB, such as in the ostium of the circumflex artery [3]. The CBL is classified according to the Medina classification [4]. As shown in Fig. 14.1, the Medina classes 1:1:1, 1:0:1, and 0:1:1 represent true bifurcations in which both branches may need intervention, depending on the size and extension of the disease in SB. PCI with drug-eluting stent (DES) is currently the standard treatment of CBL and is endorsed by the European Society of Cardiology [5].

The European Bifurcation Club (EBC) gives recommendations on how to perform CBL intervention [1, 6]. Stenting of CBL is performed using either one- or two-stent techniques (Culotte, DK [double kissing]-CRUSH, or TAP [T-and-protrusion]). The current standard recommendation is provisional stenting (PS). If SB is significant in size (usually 2.5 mm or larger) and has a lesion ≥10 mm in length, the upfront 2-stent strategy is recommended [1]. The upfront 2-stent strategy using the DK-CRUSH technique may lead to less target vessel revascularization in the distal LM CBL compared to provisional stenting [7]. The drawback of 2-stent strategies is that they are complex, time-consuming, and require high operator skills and experience. Due to a longer procedure, the radiation exposure and contrast volume are higher in complex upfront 2-stent strategies than in PS. Furthermore, two stents are more prone to late thrombosis as compared to a single stent [8]. The use of intravascular imaging is strongly recommended by the European Society of Cardiology (ESC) in complex PCI

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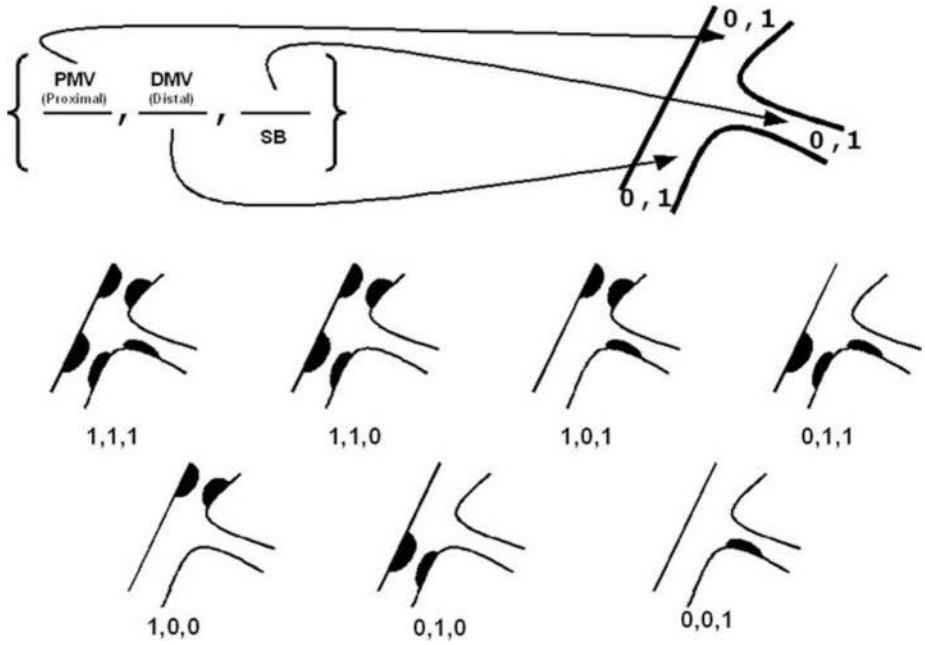


Fig. 14.1 Medina classification of coronary bifurcation lesions: 1 is used to indicate the presence of stenosis and 0 the absence of stenosis in each of the three segments. The three digits are separated by commas, PMV first followed by distal branches in order of importance (see denomination of lesions). PMV, proximal main vessel; DVM, distal main vessel. (Reprinted with permission from Louvard Y et al. [4])

involving CBL and in the LM due to better clinical outcomes including reduced mortality [9, 10].

Even though the current generation of DES performs well, they still have significant drawbacks. Firstly, the risk of acute or subacute stent thrombosis is 0.5%–3% depending on the clinical presentation of the patient, and when it occurs, results in a high mortality rate (20%–45%) [11]. Stents also cause impaired vasomotion and inflammation, which may result in late neoatherosclerosis inside the stent. The yearly rate of device-oriented adverse events after DES implantation is 3%–4% without a plateau [12]. Stenting of CBL may also cause immediate problems. First, the occlusion of SB is possible even if protected by a second wire. Second, MB stenting may cause carina shift leading to pinching of SB. Third, the crossing of stent struts with a wire may be difficult in 2-stent techniques, and sometimes the recommended final kissing balloon (FKB) inflation cannot be done. Fourth, abluminal wiring or collision of the proximal end of the stent with the guide catheter may result in unintended stent deformation, which is a complication that is often unnoticed by the operator despite the use of intravascular imaging [3].

The use of DCB may tackle some of the limitations of stenting and obviate the need for wire jailing, re-wiring, and FKB. All plaque modification options are available if restenosis occurs after DCB-only PCI, in contrast to ISR (in-stent restenosis), which limits the use of rotational or orbital atherectomy, and the previously underexpanded stent may also be resistant to intravascular lithotripsy (IVL). ISR due to an underexpanded and undilatable stent due to surrounding calcium is one of the most challenging scenarios that a PCI operator may face, leading to worse clinical outcomes. Use of the DCB-only approach in bifurcations prevents stent-related problems such as malapposition, under-expansion, and fracturing, or the overlap of multiple metal layers and polymers. Many technically demanding and time-consuming steps of complex stenting and

the formation of a metallic carina may be avoided with the DCB-only PCI in CBL.

The key advantage of a DCB-only PCI is the leaving nothing behind concept, i.e., the absence of a metallic foreign material inside arterial wall. DCB facilitates rapid and uniform antiproliferative drug transfer to the vessel wall, including the carina [13]. The vasomotion is preserved, and later lumen enlargement is enabled [14, 15]. Furthermore, DCB-only PCI requires a less aggressive antithrombotic regimen than that after stenting, which is beneficial in high-bleeding risk patients [16, 17]. The benefits of DCB-only PCI are especially anticipated to occur in the long-term follow-up by reducing myocardial infarction, the need for revascularization, and cardiovascular mortality [18, 19]. Interestingly, DCB-only PCI was found to have a 5-times lower risk of lesion thrombosis as compared to stenting using new-generation DES (HR 0.18) [20]. In multivessel disease including complex PCI such as CTOs and CBL, the reduction of overall stent burden by the DCB-oriented approach may result in better clinical outcomes as compared to the DES-only oriented approach [21].

Within the last decade, DCB has shown its potential for the treatment of de novo coronary artery lesions in all-comers registry trials [20, 22–25]. More recently, randomized controlled trials (RCTs) have shown that DCB is superior to bare metal stent (BMS) in patients at high-bleeding risk (HBR) and non-inferior to DES in small vessels [16, 26].In a recent patient-level Andromeda meta-analysis, the MACE rate was lower in the DBC-only treated patients than in patients treated with DES in small vessels. In patients at HBR, even single antiplatelet treatment has been reported to be safe after DCB-only PCI [17]. In case of severe bleeding, even all antiplatelets may be stopped, which is not possible immediately after stenting. The patient-level meta-analysis on paclitaxel DCB in coronary arteries showed lower mortality in the DCB arm at longer timepoint months, and a similar meta-analysis in peripheral artery disease demonstrated no difference in mortality between paclitaxel-coated devices as compared to other devices [18, 27].

In the recent REC-CAGEFREE-1 trial, the implantation of a DES was superior to DCB-only PCI in non-complex lesions [28]. However, in the subgroup analyses of non-true bifurcations and small vessels, both treatments performed equally, suggesting that the benefits of DCB-only PCI require more complex anatomical and clinical scenarios. This RCT was also hampered by the open-label design and a paclitaxel DCB using very small paclitaxel crystals, resulting in rapidly diminishing drug concentration in the vessel wall. The largest RCT comparing DCB and DES strategies, the SELUTION DeNovo trial, recruited 3324 patients undergoing PCI either to a sirolimus-coated balloon with nanoparticle technology with the option of bailout stenting or to the current generation of DES [29]. The primary endpoint, TLF at 1 year, was similar in both groups, fulfilling the prespecified non-inferiority margin supporting the concept of leaving nothing behind in modern PCI. The trial will have an extended three-year follow-up.

The strategies for how DCB may be used in CBL are shown in Fig. 14.2. The first is the puristic approach where either the MB alone, SB alone, or both branches are treated with the DCB-only approach. The second strategy is the hybrid (blended) approach in which DCB is used to treat the SB in the setting of a provisional bifurcation technique, either before (preferred) or after (as bailout after implantation of the MB stent). Currently, most studies of DCB in CBL have been conducted using paclitaxel DCB rather that limus-based DCB. Positive vessel enlargement appears to be more prevalent after paclitaxel-coated balloons than after sirolimus-coated balloons, but whether this reduces adverse events remains to be seen [30–32]. In recent meta-analyses, the target lesion failure (TLF) rates were similar for both balloon types [33, 34]. The next chapters discuss the evidence on the hybrid (DES + DCB) and puristic (DCB-only) approaches in CBL.

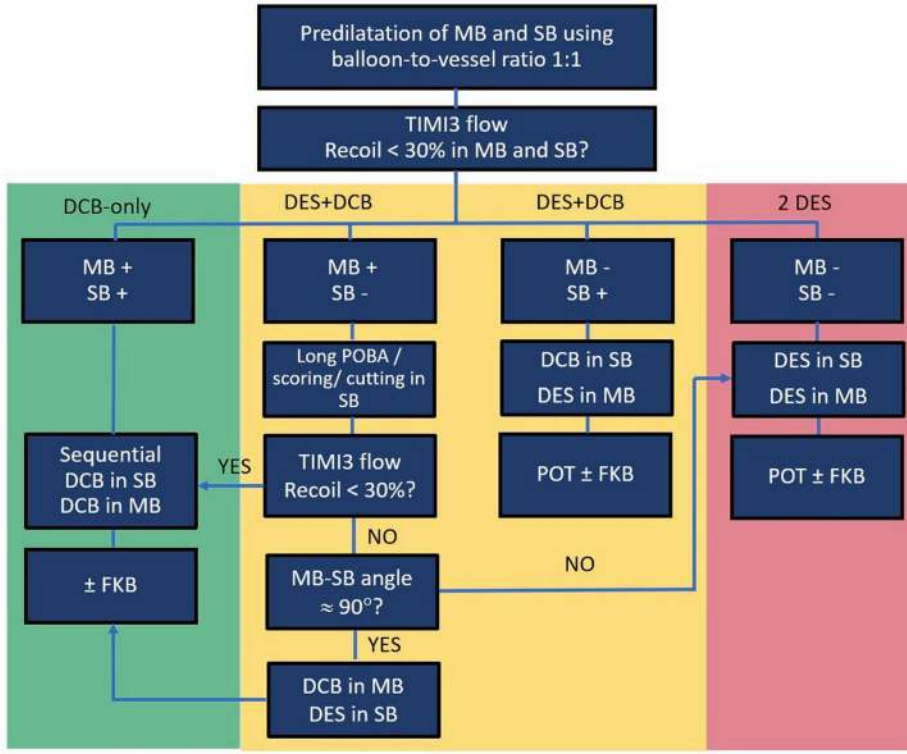


Fig. 14.2 Algorithm for treating true coronary bifurcation lesions using DCB-only, DCB + DES hybrid, or DES-only. The lesions in SB (first) and then MB (second) are predilated using 1:1 balloon-to-vessel ratio. NC balloons, scoring and cutting balloons are preferable over SB balloon for better predilatation results. Calcium debulking devices such as Rotational Atherectomy or Orbital Atherectomy or Intravascular Lithotripsy should be used according to guidelines. After predilatation, the decision on the final strategy is done based on the flow and recoil in MB and SB. If both MB and SB full the DCB-only criteria (normal flow and recoil less than 30%), sequential DCB application is recommended starting from SB. In case of substantial carina shift or pinching of either of branches, FKB may be considered (preferably with undersized balloons to prevent excess stretching of the proximal MB). If SB needs more predilatation, a long POBA inflation or special balloons should be considered to improve the result to avoid stenting of the SB. If complex stenting is to be avoided, then more than 30% recoil (depending on the SB size) may be accepted in the SB. If the SB is not acceptable for DCB treatment, it may be stented using a single stent in SB and DCB in MB in case the bifurcation angle is approx. 90°. If isolated SB stenting is not feasible, then the 2-stent strategy, e.g., using DK-CRUSH may be done. Also, the "L-sandwich" technique may be considered where the SB ostium is treated with DCB followed by a DES more distally in the SB (see text). DCB, drug-coated balloon; MB, main branch; SB, side branch; TIMI, thrombolysis in myocardial infarction (grade of blood flow); POT, proximal optimization; FKB, final kissing balloon; POBA, plain old balloon angioplasty; DK, double kissing. Colors: green = predilatation result is acceptable in both branches. Yellow = predilatation result is acceptable only in either of the branches. Red = predilatation result is acceptable in neither of the branches

14.2 The Hybrid Approach in De Novo Coronary Bifurcation Lesions

The first studies that were conducted using DCB in the CBL were done during the BMS era and are therefore outdated [35–38]. The registry-based and randomized trials of the hybrid approach combining DES in the MB and DCB treatment in the SB are listed in Table 14.1. Herrador et al. compared the use of a paclitaxel DCB (SeQuent Please, B Braun) in the SB (without proper predilatation) to conventional POBA prior to main vessel paclitaxel DES implantation

Table 14.1 Observational and randomized trials of the combination of DCB and DES (hybrid/blended approach) in coronary bifurcation lesions

Study and year	No of patients	Design	DCB type	Primary endpoint	Secondary endpoints	TLR/TVR	MACE/ MACCE	Result	Conclusion
Herrador et al. (2013) [39]	100	Prospective single-center observational study of DES in MB and DCB vs. POBA in SB in provisional T-stenting	SeQuent please (B. Braun) paclitaxel + iobromide	Restenosis and LLL at 12 months	Death, MI, TLR	12% vs. 22% ($p = 0.16$)	11% vs. 24% ($p = 0.11$)	LLL 0.09 ± 040 mm vs 0.40 ± 0.50 mm ($p = 0.01$)	DCB is superior to POBA in SB after DES in MB
SARPEDON (2015) [40]	58	Prospective multicenter single-arm observational study of DES in MB and DCB in SB	Pantera lux (Biotronik AG)paclitaxel + BTHC	Restenosis at 6 months	TVR and MACE at 12 months	3.0%	19%	6% restenosis in SB	DES in MB and DCB in SB is safe and effective
BIOLUX-I (2015) [41]	35	Prospective multicenter single-arm observational study of DES in MB and DCB in SB	Pantera lux (Biotronik AG) paclitaxel + BTHC	LLL in SB at 9 months	MACE and TVR at 12 months	2.9%	5.7%	LLL 0.10 ± 0.43 mm in SB	DES in MB and DCB in SB is safe and effective
DEBSIDE (2015) [42]	52	Prospective multicenter single-arm observational study of DES in MB and DCB in SB	Danubio balloon (Minvasys) paclitaxel + BTHC	LLL in SB at 6 months	LLL in MB, binary restenosis and TLR	2.0%	n.r.	LLL 0.04 ± 0.34 mm in SB	Low LLL and restenosis rate after DES in MB and DCB in SB
BEYOND (2020) [43]	222	Multicenter RCT of DES in the MB and DCB vs POBA in the SB	Bingo (Yinyi Biotech) paclitaxel + iohexol matrix	Target vessel stenosis in SB at 9 months	TLR, TVR, MACE	0% vs. 0%	0.9% vs. 3.7% ($p = 0.16$)	Target vessel stenosis 29% vs. 40% ($p < 0.0001$)	DCB is superior to POBA in SB after DES in MB

(continued)

Table 14.1 (continued)

Study and year	No of patients	Design	DCB type	Primary endpoint	Secondary endpoints	TLR/TVR	MACE/ MACCE	Result	Conclusion
Li et al. (2021) [44]	219	Retrospective single-center observational study of DES in MB and DCB vs. POBA in SB	SeQuent please (B. Braun) paclitaxel + iobromide	LLL in SB at 12 months	Restenosis, MACE, MI, CV death	n.r.	13% vs. 24% ($p = 0.033$)	LLL 0.11 ± 0.18 mm vs. 0.19 ± 0.25 mm (0.024)	DCB is superior to POBA in SB after DES in MB
Liu et al. (2022) [45]	100	Retrospective single-center observational study of DES in MB and DES vs. DCB in SB	Bingo (Yinyi biotech) paclitaxel + iohexol matrix	LLL in SB at 6 months	MACE, TLR	6% vs 12% ($p = 0.485$)	6% vs. 14% (p = n.r.)	LLL −0.17 mm vs 0.43 ($p < 0.001$)	Combination of DES and DCB is safe and effective for the treatment of LM bifurcation lesions
Pan et al. (2022) [46]	597	Retrospective single-center propensity-matched observational study of DES in LM bifurcation using DES MB and DES vs. DCB in SB	SeQuent please (B. Braun) paclitaxel + iobromide	Composite of TLF: CV death, TV-MI and CD-TLR at 24 months	–	2.9% in DCB vs. 9.4% DES	–	TLF 7.6% in DCB vs 14% in DES	The combination of DES and DCB is safe and effective for the treatment of LM bifurcation lesions
Ikuta et al. (2022) [47]	138	Prospective multicenter single-arm observational study of DES in MB and DCB in SB	SeQuent please (B. Braun) paclitaxel + iobromide	Binary restenosis at 12 months	TLR, MACE, LLL	3.6%	2.9%	Binary restenosis 8.0% in SB	DCB size relative to the reference vessel diameter is a predictor of late lumen enlargement in SB

Kasbaoui et al. (2023) [48]	45	Prospective single-center single-arm observational study of DES in MB and DCB in SB	Agent (Boston Scientific), paclitaxel + acetyl tributyl citrate	TLF at 6 months	Technical success	2.2%	2.2%	TLF 2.2%	DES in MB and DCB in SB is safe and effective
EASTBOURNE-BIF (2024) [49]	194	Substudy of prospective multicenter single-arm observational study of DES in MB and DCB in SB or DCB-only	MagicTouch (concept medical) sirolimus + phospholipid	TLR at 12 months	All-cause mortality, MACE, MI	4.2%	8.8%	Similar outcomes as compared to non-CBL in the same study	First study on sirolimus-coated balloon in CBL
DCB-BIF [50]	784	Multicenter RCT of DES in the MB and DCB vs POBA in the SB	Paclitaxel DCB	MACE at 12 months	All-cause mortality, CV death, MI, clinically driven TLR or TVR, angiographic and clinical/procedural success, and crossover from 1 stent to 2 stents	1.3% vs 1.5%	7.2% vs. 12.5%	Less MACE ($p = 0.013$) driven by MI (5.6% vs. 10.9%, $p = 0.008$)	DCB in SB ostium compared to POBA reduces MACE driven by MI

DCB drug-coated balloon, *DES* drug-eluting stent, *MB* main branch, *SB* side branch, *MI* myocardial infarction, *TLR* target lesion revascularization, *TLF* target lesion failure, *CV* cardiovascular, *TVR* target vessel revascularization, *MACE* major adverse cardiovascular events, *POBA* plain old balloon angioplasty, *LLL* late lumen loss, *n.r.* not reported, *RCT* randomized controlled trial

(Taxus Liberté) in 100 patients needing provisional T-stenting [39]. In the event of a suboptimal SB result, either DES (4% in the POBA group, 4%) or BMS (10% in the DCB group) were used as bailout stents. The incidence of SB restenosis at 12 months was numerically lower within the DCB group (7%) than in POBA group (20%). LLL in SB was significantly lower in the DCB group as compared to POBA group.

The concept of DCB at the SB ostium after DES implantation in the MB was further tested in the single-arm prospective registry SARPEDON study, which included 58 patients with 41% of true CBL [40]. LLL was 0.09 mm and the restenosis rate 6% in SB. Despite good angiographic outcome and low restenosis rate, the rate of MACE rate was unexpectedly high at 1 year (19%). The BIOLUX-I study was a prospective, multicenter study conducted in 35 patients with CBL of 2.0–4.0 mm in diameter to assess the feasibility of the hybrid approach in CBL with a combination of DES in the MB and DCB in the SB [41]. The DCB used was paclitaxel (Pantera Lux, Biotronik). Late lumen loss at prescheduled nine-month angiography was low (0.10 ± 0.43 mm) in the SB with no binary restenosis. One target lesion revascularization occurred by 12 months (2.9%). The authors concluded that this novel approach is safe and effective for the treatment of CBL. The prospective observational multicenter DEBSIDE study investigated the efficacy of a Danubio paclitaxel DCB in the SB after implantation of a DES in the MB in 52 patients with CBL (66% true) [42]. The study showed that DCB in SB is safe and effective with very low LLL and clinical restenosis rate (2% in SB) at 6 months. The limitation of the SARPEDON, DEBSIDE, and Biolux-1 studies was that there was no control treatment (i.e., POBA or DES in the SB). Similar observational studies on the DCB in the SB combined with MB stenting have been recently published [48, 51]. Recently, in a propensity-matched observational study, the use of DCB in the LCX ostium resulted in similar TLR as compared to stenting, but the radiation dose and amount of contrast agent was less [43]. Moreover, the lack of metal in the LCX ostium enables easier reinterventions.

BEYOND was the first large, randomized study of a paclitaxel DCB (Bingo, Yinyi Biotech, Dalian, China) to POBA for SB disease following MV DES implantation followed by KBI [52]. Approximately 90% of the 222 recruited patients had Medina 1:1:1 disease. At 9-month follow-up, target lesion stenosis of the SB was 28.7% vs 40.0% ($p < 0.001$), in favor of DCB treatment. There was evidence of positive vessel remodeling in the DCB group with LLL of −0.06 vs 0.18 mm ($p < 0.001$). MACCE had a lower trend in the DCB cohort at 0.9% vs 3.7% ($p = 0.16$). Li et al. investigated DCB vs. POBA in SB after MB stenting with DES in 219 patients [51]. LLL was less, and there was a decrease in MACE (13% vs. 24%, $p = 0.033$) when SB was treated with DCB instead of POBA.

Liu et al. retrospectively enrolled 100 patients with true LM CBL that were divided into two DES groups (both MB and SB) and DES in MB and DCB in SB group [45]. In the hybrid DES + DCB group, in most of the patients, the MB stent was first implanted with subsequent DCB treatment in SB. Various techniques were allowed in the two-stent group. In both groups, FKB was done. The MLD in the LCX ostium was higher in the DES + DCB group than that of the two DES groups. Late lumen loss (LLL) was smaller in the LCX ostium in the DES + DCB group than in the DES group ($p < 0.05$). The incidence of MACE was similar in the two groups. Authors concluded that hybrid approach DES in MB and DCB in SB was safe and effective in the treatment of true LM CBL. The hybrid approach using DES in MB and DCB in SB of LM is shown in Fig. 14.3.

Pan L et al. reported the clinical and angiographic outcomes of patients with distal LM true CBL treated with DES + DCB hybrid approach in a propensity-matched population of nearly 600 patients: 199 patients received DCB in SB and DES in MB and 398 were assigned to DES-only strategy (either provisional stenting or two-stent

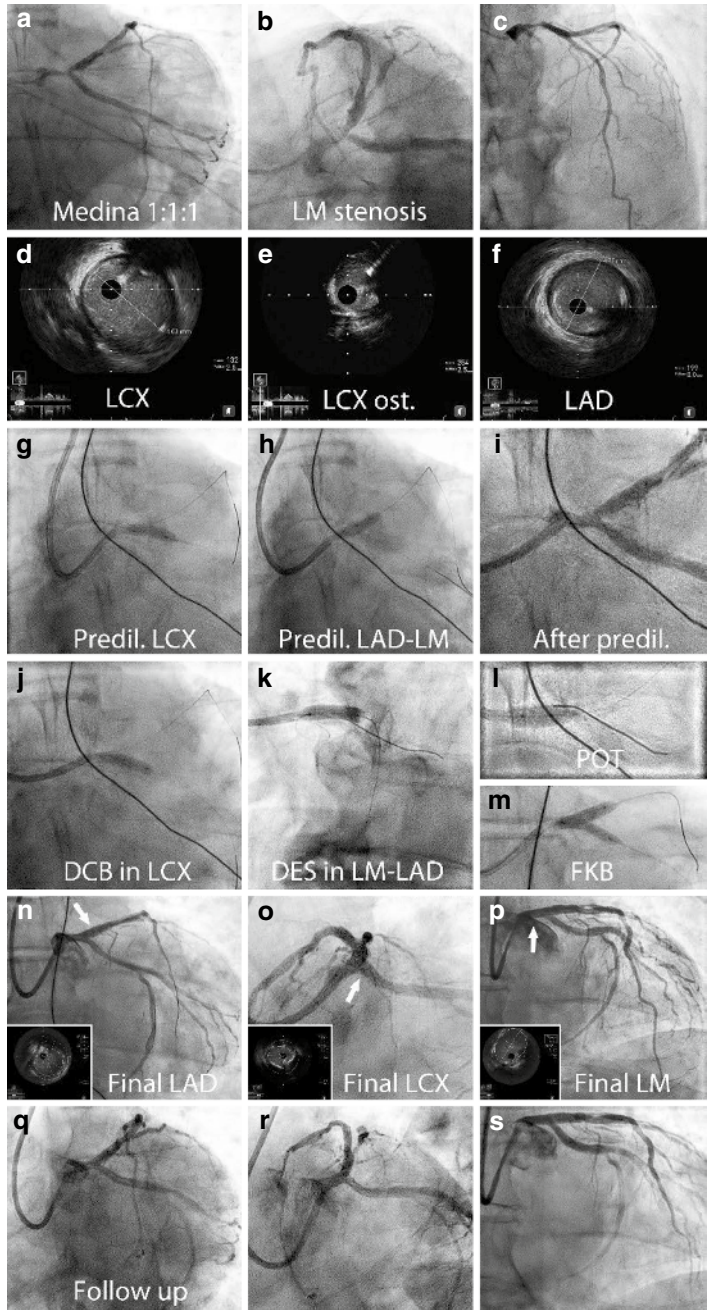


Fig. 14.3 The hybrid (blended) DCB + DES approach in true LM bifurcation lesion. 71 years old male with CCS class 2 stable angina was admitted for coronary angiography. (**a**–**c**) Medina 1:1:1 LM bifurcation lesion. (**d**–**f**) IVUS was used to assess the lesions, showing a tight stenosis in the LCX ostium. (**g**, **h**) Predilatation of LAD, LCX, and LM was done using 4.0 mm cutting balloon. (**i**) The predilatation result was satisfactory for LCX (normal flow and less than 30% recoil), but there was unacceptable recoil in the LM (assessed by IVUS). (**j**) First, 4.0 × 15 mm paclitaxel DCB was applied in the LCX for 30 s. (**k**) Thereafter, 5.0 × 16 mm DES was implanted from LM ostium toward LAD, followed by (**l**) POT using 5.5 × 6 mm NC balloon and (**m**) FKB using 4.0 mm and 3.5 mm NC balloon in LAD and LCX, respectively. (**n**–**p**) Final result. Arrows show where IVUS (inset) was obtained. Minimal lumen areas were 14 mm^2, 7.7 mm^2, and 19.5 mm^2 in LAD, LCX, and LM, respectively. (**q**–**s**) Follow-up angiography PCI shows a good angiographical result 3 months after the hybrid DCB + DES PCI. CCS, Canadian Cardiovascular Society; LM, Left Main; LAD, Left Anterior Descending Artery; LCX, Left Circumflex Artery; IVUS, Intravascular Ultrasound; DCB, Drug-Coated Balloon; DES, Drug-Eluting Stent

strategies) [53]. TLF occurred in 7.6% assigned to DCB group and in 14% assigned to DES group at 2 years. Cardiac death, target vessel myocardial infarction, all-cause mortality, and stent thrombosis rates were similar between both groups. Patients treated with the DES-only approach were associated with a higher LLL compared with the DCB in the SB at 1 year, probably due to frequent use of POBA in the SB in the DES group. In the sensitivity analysis, the DCB group also presented a lower incidence of target lesion and vessel revascularization as well as stent thrombosis, both compared to the DES-only strategy ($p < 0.05$).

In a substudy of the HYPER trial, 50 patients with true CBL were treated with the hybrid strategy, i.e., DES in MB and DCB in SB [47]. This study suggests that such a hybrid strategy is a safe and effective option for two stents in true CBLs. Finally, Ikuta et al. demonstrated that in 72% of cases late lumen enlargement occurs in the SB ostium after paclitaxel-coated DCB administration [54]. They also showed that the DCB size in SB relative to the reference vessel diameter is a predictor of late lumen enlargement in SB, meaning that adequate balloon sizing is important for SB treatment with DCB.

The hybrid approach of two-stents and DCB ("L-sandwich") strategy has been recently described in a small RCT: this means the implantation of a stent in the MB, the treatment of SB ostium with DCB, followed by the implantation of a stent to the SB without covering the carina with struts [49]. This simplistic two-stent approach was observed to achieve comparable angiographic results as compared to designated two-stent strategies and to the hybrid DES + DCB approach. The theoretical benefits as compared to traditional 2-stent strategies include a simpler procedure, less metal in the carina and MB as well as no risk for too much SB stent protrusion in the MB.

The EASTBOURNE-BIF substudy included 194 patients treated with either the hybrid (blended) or the DCB-only approach. When compared to non-CBL lesions, the clinical endpoints were similar in CBL lesions, including TLR, MACE, all-cause mortality, and MI [55]. The authors concluded that sirolimus-coated DCB alone, or in combination with DES, could represent a safe and effective alternative to stents for the treatment of CBL.

The largest RCT on the use of DCB in CBL, the DCB-BIF trial, randomized patients (n = 784) with non-LM bifurcation lesions to either receive paclitaxel DCB or POBA if the SB diameter stenosis was greater than 70% after main vessel DES placement [56]. The primary endpoint, MACE at 12 months, was significantly lower in the DCB arm (7.2%) than in the POBA arm (12.5%), driven by less target vessel MI in the DCB group (5.6% vs. 10.9%). Surprisingly, there was no difference in the TLR rates between the groups. The DCB-BIF trial has limitations. The trial included only simple CBL, as the extent of SB disease was less than 10 mm, meaning that the complex CBL were excluded. No special balloons were allowed before DCB treatment. The DCB used in the trial are not stated in the publication. Finally, the reason for less target vessel MI without less TLR or TVR in the DCB arm remains unclear [57].

The recent meta-analysis conducted by Rocchetti et al. comprising two RCTs and three observational studies ($n = 1762$) showed that the use of DCB in the SB significantly reduced MACE (OR = 0.48) and MI (OR = 0.39) compared to use of POBA in the SB of CBL, while no difference was found in TLR or TVR [58]. Taken together, the DCB treatment in the SB of CBL combined with MB stenting is safe and results in fewer MACE as compared to POBA.

14.3 DCB-Only Approach for De Novo Coronary Bifurcation Lesion

The DCB-only approach is appealing in CBL as it results in the "leaving nothing behind" concept with all the advantages discussed previously. The currently published observational and randomized studies on this novel approach are shown in Table 14.2.

Shulz et al. were pioneers in the field as they treated CBL including LM and proximal LAD with the DCB-only strategy in a small pilot study of 39 patients, suggesting that it is safe and results in an acceptable TLR rate of 7.7% [59]. Bruch et al. recruited 127 patients in a prospective multicenter registry study with CBL including an SB > 2 mm in diameter of any Medina class [66]. The DCB-only approach was targeted in both MB and SB with the possibility of bailout BMS in case of flow-limiting dissection or significant recoil. 54% of patients underwent the DCB-only strategy, 35% one BMS in the MB, 8.5% BMS in SB, and 3.1% two stents (both MB and SB). At 9 months, the TLR rate was 4.5%, and the MACE rate was 6.1%. More recently, Ke et al. randomized 60 patients with true CBL either to a standard two-stent strategy or a DCB-only strategy in a pilot study [62]. LLL at 12 months was significantly better both in MB and SB with positive remodeling in the SB (negative LLL). The study was underpowered for clinical endpoints but demonstrated the feasibility of this simple approach to a complex anatomical scenario.

PEPCAD-BIF randomized 64 patients to either DCB or POBA for distal MB or isolated SB disease. Mainly small vessels (mean diameter 2.4 mm) were included in the trial [67]. The primary endpoint, late lumen loss (LLL), was significantly lower in the DCB than in the POBA group. Restenosis rate was only 6% in the DCB group vs 26% in the POBA group. A recent focused meta-analysis by Corballis et al. showed that DCB was found to be superior to POBA for SB treatment, and for the MB it was found to be a safe alternative to stenting [68]. Moreover, Zheng et al. included 934 patients from ten studies (five RCTs) showing that DCB in SB is associated with less LLL, a lower rate of binary restenosis as well as less MACE as compared to POBA [69].

The single stent strategy may cause as high as a 20% restenosis rate in the SB [61]. In contrast, local drug delivery by DCB in the MB appears to induce beneficial enlargement also in the SB ostium as studied using optical coherence tomography (OCT) [70]. The same group has thereafter shown that DCB treatment on the MB demonstrated favorable angiographic enlargement in the SB ostium, whereas DES implantation in the MB or optimal medical therapy did not cause this effect 6–9 months after PCI [71]. Therefore, the DCB-only PCI in the MB alone may be a simple and effective approach to CBL treatment if the SB is small and the disease is restricted to the ostium.

An interesting target for DCB-only PCI is the LM bifurcation [64]. Currently, there are only observational data on the use of DCB-only PCI in the LM CBL [60, 63, 65, 72]. These small studies suggest that the stentless approach in the LM is safe. However, adequate lesion preparation is of utmost importance to reduce the TLR rate [65]. Patients with HBR or with poor antiplatelet drug adherence could benefit from the stentless PCI strategy. The DCB-only approach in a calcified LM bifurcation is demonstrated in Fig. 14.4.

According to the EBC recommendation, the inverted PS should be used for Medina 0:0:1 (isolated SB stenosis) CBL. However, stenting of the SB may cause compromise to the MB. Therefore, the DCB-only treatment of Medina 0:0:1 lesions, such as ostial LCX or the first diagonal branch, could offer a better alternative. Vaquerizo et al. included 49 patients with isolated (Medina 0:0:1) CBL that were treated by the DCB-only approach [73]. Predilatation with a cutting balloon was used in 59% of the cases, a method that usually gives an adequate predilatation result in the SB ostium. Binary restenosis occurred in 23% of cases at 7 months. The rate of bailout stenting was quite high (14%). Authors concluded that DCB-only approach was a safe and technically feasible therapeutic option in isolated SB stenosis. Figure 14.5 shows this very simple and effective approach for isolated SB stenosis.

Table 14.2 Observational studies of DCB-only approach in coronary bifurcation lesions

Study	No of patients	Design	DCB type	Primary endpoint	Secondary endpoint	TLR/TVR	MACE	Result	Conclusion
Schulz et al. (2014) [58]	39	Retrospective single-arm single-center observational study of DCB in both MB and SB	SeQuent please (B Braun) or InPact falcon, (Medtronic)	Binary restenosis at 4 months	MACE, TLR	7.7%	7.7%	Binary restenosis 10% (all in LM CBL)	DCB-only PCI in CBL is safe
Bruch et al. (2016) [59]	127	Prospective multicenter single-arm study of DCB-only vs DCB + BMS	SeQuent please (B Braun)	TLR at 9 months	MACE	4.5% vs. 3.6% ($p = 0.80$)	6.1% vs. 7.3% ($p = 0.79$)	Similar outcome between the groups	DCB-only PCI in CBL is safe
Vaquerizo et al. (2016) [60]	49	Prospective single-center single-arm study of DCB-only in isolated SB	Dior (Eurocor)	MACE, restenosis, LLL	TLR	14%	16%	Restenosis 23% and LLL 0.32 ± 0.73 mm at 7 months	DCB-only PCI is feasible in isolated SB lesion
Her et al. (2016) [61]	16	Prospective single center single-arm study of DCB-only in isolated SB	SeQuent please (B Braun)	SB ostial lumen area at 9 months (OCT)	MLD	n.r.	n.r.	Net gain in ostial SB: 0.6 ± 0.93 mm^2 (+76%)	DCB in MB results in ostial SB lumen area
PEPCAD-BIF (2016) [62]	64	Multicenter RCT of DCB-only vs. DES in distal MB and SB	SeQuent® please (B Braun Germany)	LLL at 9 months	TLR, binary restenosis	3.1% vs 9.4%	n.r.	0.13 mm ± 0.31 in DCB vs 0.51 ± ± 0.66 in POBA ($p = 0.013$). Binary restenosis rate 6% vs. 26% ($p = 0.045$)	DCB is superior to POBA in distal MB and SB
Liu et al. (2022) [63]	85	Retrospective single-center study of DCB-only vs. DES in LM	Bingo (Yinyi Biotech) paclitaxel + iohexol matrix	MACE at 12 months	LLL and MLD	9.7% vs. 18% ($p = 0.351$)	9.7% vs. 18% ($p = 0.351$)	No difference in restenosis in clinical endpoints	DCB-only PCI in LM is safe

Uskela et al. (2023) [64]	66	Retrospective single-center single-arm study of DCB-only in LM	Paclitaxel DCB	MACE at 12 months	TLR	6%	24%	TLR only 1.9% if lesion prep done according to consensus group recommendation	DCB-only PCI in LM is safe
Gunawardena et al. (2023) [65]	148	Retrospective single-center propensity-matched study of DCB-only vs. DES in LM	SeQuent please (B Braun)	All-cause mortality	CV mortality, MI, TLR	7.3% vs 8.3% ($p = 0.86$)	n.r.	All-cause mortality 20% vs. 15% ($p = 0.42$)	DCB-only PCI in LM is safe
Ke et al. (2023) [66]	60	Single center RCT of DCB-only PCI vs. two DES in true CBL	SeQuent please (B Braun)	LLL at 12 months	MACE	0% vs. 0%	6.7% vs. 13.3% ($p = 0.667$)	LLL 0.05 ± 0.24 mm vs. 0.25 ± 0.35 in MB ($p = 0.013$) and − 0.02 ± 0.19 vs. 0.11 ± 0.15 in SB ($p = 0.005$)	DCB-only PCI is safe in true bifurcations

DCB drug-coated balloon, *LM* left main, *DES* drug-eluting stent, *MB* main branch, *SB* side branch, *MI* myocardial infarction, *TLR* target lesion revascularization, *TLF* target lesion failure, *CV* cardiovascular, *TVR* target vessel revascularization, *MACE* major adverse cardiovascular events, *POBA* plain old balloon angioplasty, *LLL* late lumen loss, *n.r.* not reported, *CBL* coronary bifurcation lesion, *RCT* randomized controlled trial, *MLD* minimal luminal diameter

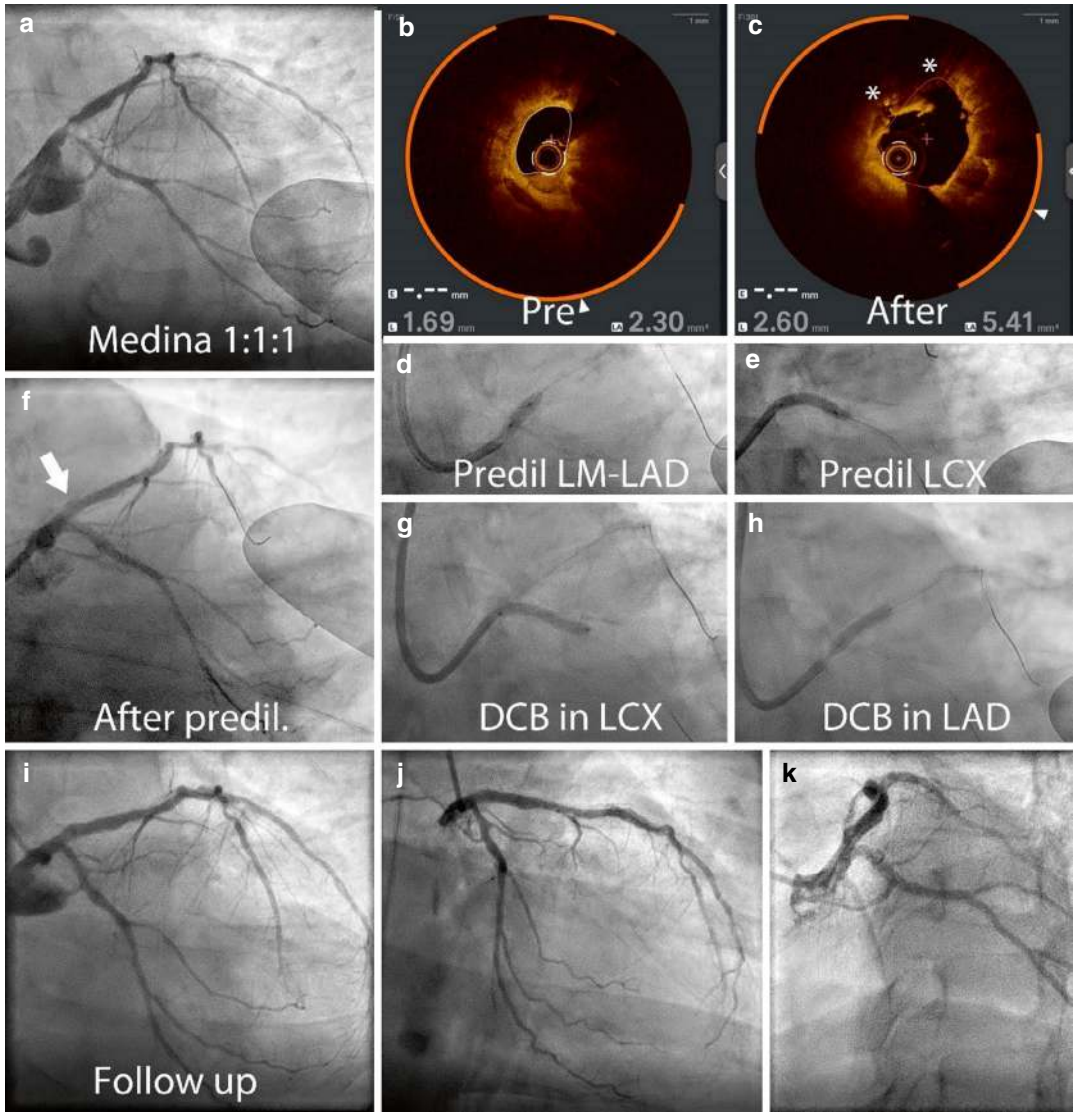


Fig. 14.4 DCB-only approach in the LM bifurcation lesion. (**a**) Coronary angiography in 74 years old female with CCS class 3 exertional angina revealed a Medina 1:1:1 calcified LM bifurcation lesion. (**b**) Optical coherence tomography (OCT) showed circumferential calcium that needed debulking. (**c**) After orbital atherectomy and predilatation, OCT demonstrated cracks in the calcium (asterisks). (**d**) 3.5 mm cutting balloon was used for predilatation in the proximal LAD and LM. (**e**) 3.25 mm non-compliant balloon was used for predilatation of the LCX. (**f**) After orbital atherectomy and predilatation, there is a non-flow-limiting dissection in the proximal LAD (arrow) suggesting a favorable long-term outcome. (**g**) The proximal LCX was treated using 3.0 × 20 mm Paclitaxel-coated DCB and H) the proximal LAD using a 3.5 × 15 mm Paclitaxel-coated DCB, both for 30 s. (**i–k**) Control angiography 2 months after the DCB-only approach showed the healing of dissections and positive remodeling both in the LCX and LAD. CCS, Canadian Cardiovascular Society; DCB, drug-coated balloon; LM, Left Main; OCT, Optical Coherence Tomography; LAD, Left Anterior Descending Artery; LCX, Left Circumflex Artery

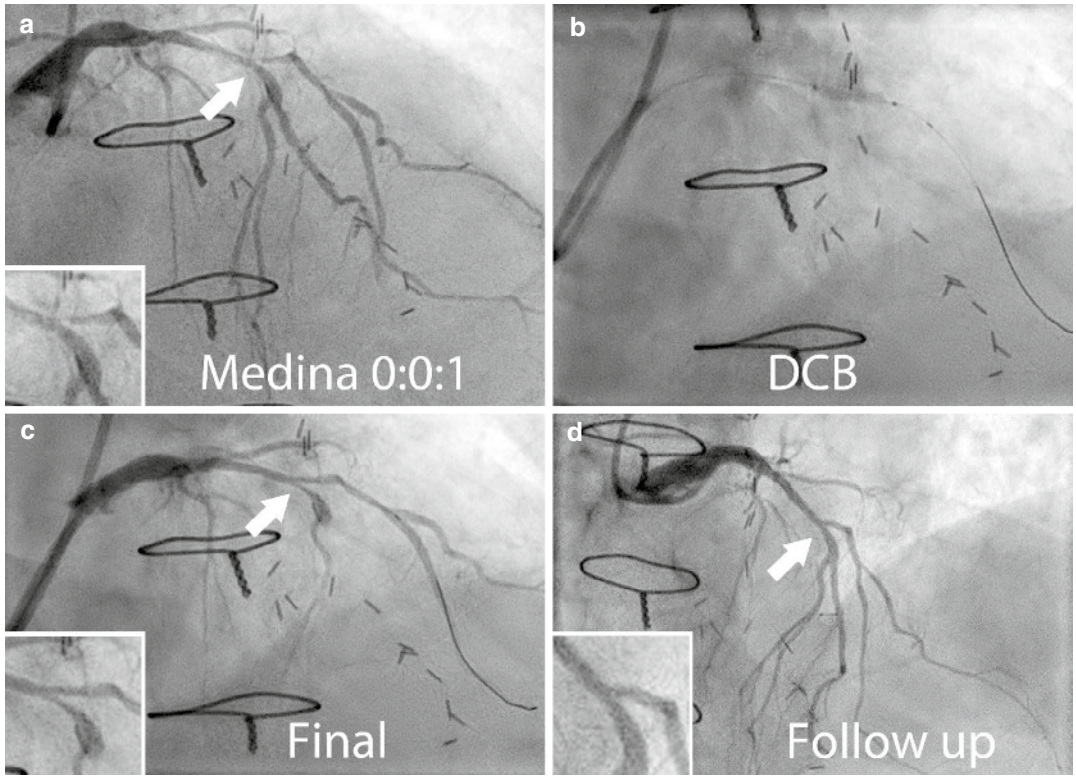


Fig. 14.5 Treatment of isolated ostial lesion in the SB (Medina 0:0:1) using the DCB-only approach. 75 years old male with previous CABG was admitted to hospital due to unstable angina. (**a**) Coronary angiogram showed a lesion in the ostium of the D1 (arrow) which was not grafted. (**b**) The lesion was predilated using a 2.5 mm NC balloon followed by treatment with paclitaxel-coated DCB of the same size. (**c**) The final result (arrow) was acceptable (less than 30% recoil and normal blood flow). (**d**) Angiography 2 years after the DCB-only PCI showed a good long-term result. Stenting of a Medina 0:0:1 lesion usually requires a stent extending to MB, possibly compromising MB. CABG, coronary artery bypass grafting; DCB, drug-coated balloon; SB, single branch; MB, main branch

In the SELUTION DeNovo trial (n = 3324), approximately a third of the treated lesions involved a CBL, and in this prespecified subgroup analysis, the use of the DES or DCB strategy resulted also in similar TLF at 1 year [29]. An important finding of the trial was also that over 80% of all lesions could be safely treated using DCB-only strategy. These findings support the concept of leaving nothing behind in CBL.

14.4 Bifurcation ISR

Repeat PCI in ISR is associated with worse outcomes as compared to de novo lesions, and PCI in CBL is linked with higher restenosis rates as compared to non-CBL lesions [7]. Naganula et al. reported clinical outcomes of 158 patients with ISR involving CBL treated either with DCB or second-generation DES [74]. There was no

significant difference in MACE between the two groups in the median follow-up period of 701 days. Harada et al. studied PCI using DCB in a bifurcation ISR of two previously implanted stents (66% SB, 26% MB distal and 8% MB proximal) [75]. In this study, two types of paclitaxel-coated balloons, with either an iopromide or a butyryl tri-n-hexyl citrate excipient, were used. The binary restenosis and MACE rates were 24% at 12 months. No stent thrombosis occurred after re-PCI. The outcomes of LM ISR treated either with DCB and DES were reported by Lee et al. [76]. While similar TLR rates were found, a significantly higher cardiovascular mortality was found in the DES group as compared to the DCB group. In most cases, DCB treatment of bifurcation ISR is reasonable to avoid further metallic implants in an already very complex situation. Intravascular imaging should always be used to optimize ISR treatment [9].

14.5 How to Use DCB in Coronary Bifurcations?

Lesion preparation is the most important step in DCB-only PCI, and CBL makes no exception. The optimal lesion preparation before DCB application is discussed more in detail elsewhere in this book. The challenges in DCB-only PCI include the risk of recoil or flow-limiting dissection. Recoil left after DCB-only PCI is a major risk factor for restenosis [65, 77]. Minor dissections (Type A or B, i.e., without contrast hanging in the lesion) and residual stenosis <30% are acceptable [19, 78]. In small vessels and the SB ostium, even higher recoil may be acceptable considering the potential downsides of stenting (e.g., in isolated Medina 0:0:1 CBL). The dissection of the medial layer is required for good late lumen enlargement and favorable clinical outcomes after DCB-only PCI [31, 79]. During predilatation, the balloon-to-vessel ratio should be 1:1. Using of intravascular imaging may be beneficial for achieving optimal lesion preparation in DCB-only PCI in complex anatomical situations to help understand underlying vessel pathology, the correct sizing of predilatation balloon, and the need for calcium modification [44]. Recently, it was shown that the use of IVUS-guided DCB angioplasty was superior to an angio-guided procedure in terms of LLL [80]. The final strategy: DCB-only, DES-only, or the DES + DCB hybrid approach cannot be determined before intervention, but it is based on the predilatation result (Fig. 14.2). The hybrid approach using DES and DCB in MB and SB, respectively, is shown in Fig. 14.3. DCB inflation should last at least 30 s, but preferably 60 s, for efficient drug transfer. However, the patient may not tolerate a balloon inflation longer than 15–20 s in the LM bifurcation and therefore sequential shorter inflations can be performed (Fig. 14.4).

Non-compliant, scoring, and cutting balloons often provide better predilatation results with less risk of major dissections compared to semi-compliant balloons. Scoring balloons seem to be beneficial for reducing recoil and preventing major dissections in de novo lesions [81]. Cutting balloons often work well for fibrocalcified lesions. Both scoring and cutting balloons are preferred for optimal preparation in ostial side branch lesions and can be used to release subintimal hematoma (type C dissection). The threshold for calcium modification to reduce the volume of calcium should be low to reduce the risk of recoil and improve drug transfer. Long inflations may seal dissections and result in improved luminal gain. Paclitaxel, as a lipophilic drug, seems to work very well in calcified lesions after rotational or orbital atherectomy [82, 83]. Intravascular lithotripsy is a useful tool for concentric calcified lesions and can be used before DCB-only approach (Rissanen TT et al., unpublished). In Japan, directional coronary atherectomy was used successfully in combination with DCB-only (with a TVF rate of 3.2% at 12 months) in a small observational study in the left main (LM) bifurcation [84]. A Chinese group has developed a scoring system for the prediction or poor outcomes after DCB-only PCI [85]. The study identified seven independent factors, including calcified lesions, true bifurcation lesions, immediate lumen gain rate (<20%), immediate diameter stenosis (>30%), DCB diameter/reference vessel diameter ratio (<1.0), DCB length, and

mild dissection. These factors are important in determining whether additional lesion preparation is necessary and whether the MB requires a stent. Another study demonstrated that inadequate lesion preparation in ISR lesions more than doubled the risk of TLR compared to optimal lesion preparation [86].

In true CBL, the DCB-only treatment should usually be done first in the SB and then in the MB to prevent carina shift toward the more important branch. Routine kissing DCB is not recommended in CBL treatment because of the reduced contact area of the balloons to the vessel wall and the increased risk of overdilatation and dissection of the proximal MB, and because the interaction of DCB may cause loss of the drug. If there is a substantial carina shift leading to severe pinching or reduced flow in either of the branches after sequential DCB treatment, a gentle FKB may be considered after DCB treatments. However, due to the lack of a metallic implant, the carina shift will probably be corrected in the follow-up even without an additional FKB. If the SB needs intervention after the stenting of the MB in the hybrid approach, it may be predilated again and then treated with an adequately sized DCB. Finally, re-POT (i.e., POT-side-POT) or FKB should be done at the operator's discretion.

Similar to stent-based strategies, provisional DCB strategy is preferable when there is no significant disease in the SB (non-true CBL). The SB ostium will improve after treatment with a paclitaxel-coated DCB in the MB, and the pinching of the SB ostium without flow disturbance does not require intervention [70].

14.6 Future Directions

The promising results from literature suggest that the hybrid approach, combining DES and DCB, as well as the puristic approach of leaving nothing behind, is fundamentally changing the treatment for CBL. However, no adequately sized randomized controlled trials have been published to date to compare the DCB-only strategy with the DES strategy in CBL. The EBC-DCB trial (n = 750) is ongoing in Europe and Korea and compares the DCB-only approach with the possibility to bailout stenting to the standard of care, which is the DES-only approach (NCT06822322). The primary endpoint of the trial is the non-inferiority of cardiovascular death, target bifurcation-related myocardial infarction, or target bifurcation revascularization at 1-year. Another ongoing trial, PICCOLETO-V comparing PCB vs SCB vs DES in native bifurcation lesions (NCT06551662). The primary outcome is 6–9 Months % maximum stenosis CT-FFR or Invasive FFR guided in bifurcation lesions.

As the population in the Western World ages, the volume of PCIs in octogenarians will increase in the future [87]. Currently, 40–50% of patients needing PCI are at HBR [88]. At least 1-month dual antiplatelet treatment (DAPT) is mandatory after stenting. However, after complex PCI such as after a two-stent strategy, the DAPT duration is usually longer (often at least 6 months). In addition, in this situation, DAPT cannot be safely terminated within the first 4 weeks in case of bleeding or due to the need for urgent surgery. One of the major advantages of the DCB-only strategy is that the antiplatelet treatment may be shortened after DCB-only PCI in bifurcations. Preliminary data suggest that even SAPT may be used after DCB-only PCI in HBR patients [17, 89]. This novel concept is being tested in the DEBATE RCT including CBL (NCT04814212).

14.7 Conclusions

The use of DCB in complex anatomical scenarios such as in CBL is one of the most promising indications for this technology [89]. In CBL, the use of DCB simplifies the procedure and may lead to more favorable long-term outcomes as compared to the use of DES-only [19, 44, 46, 50, 90]. The major advantages of DCB in CBL are: (1) homogeneous drug transfer to the vessel wall, lasting for weeks; (2) the absence of a permanent implant, reducing the risk of acute or late vessel thrombosis and neoatherosclerosis; (3) allowing for maintaining the original geometry of the carina and vasomotion of the vessel; (4) Shortening of DAPT or even SAPT after PCI, which is beneficial in

patients at HBR; (5) the reinterventions are more feasible due to the lack of metallic stent layers.

The hybrid approach, i.e., the application of DCB in the SB in addition to MB stenting if needed, is appealing for its less complex nature and avoidance of multiple metal layers in the proximal MB. However, the puristic approach of leaving nothing behind, i.e., treating both branches with DCB, could be the best option in the long-term, especially after an optimal predilatation result. If the bioabsorbable scaffolds improve in material technology and allow CBL interventions, they may replace metallic DES, allowing the "leaving nothing behind" approach in most cases.

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The Role of Drug-Coated Balloons in a Blended Fashion with DES

15

Eun-Seok Shin

Multivessel CAD accounts for approximately 30%–40% of patients with coronary artery disease, and its management poses significant challenges. Multivessel CAD benefits significantly from revascularization through PCI, showing a higher rate of freedom from adverse cardiovascular events with complete revascularization compared with incomplete revascularization [1]. In DCB trials, small-vessel disease has commonly been defined as a reference vessel diameter of ≤2.75 mm or <3.0 mm, depending on the study, and selected clinically significant small-vessel lesions may require PCI to achieve complete revascularization. However, the effectiveness of DES in these small vessels, especially over the long term, remains limited by small luminal diameter and cumulative metal burden. While the long-term safety and efficacy of DES are well established, there are concerns about late adverse events associated with the presence of a permanent rigid metallic cage. Additionally, in the era of second-generation DES, the presence of multivessel disease, the need for multiple stents, and the use of long stents remain significant predictors of ischemic clinical events in patients undergoing PCI [2].

Drug-coated balloon (DCB) treatment is an established option for coronary in-stent restenosis and has shown favorable outcomes over plain balloon angioplasty [3]. In de novo small-vessel disease, randomized trials have demonstrated noninferiority, and in selected data superiority, compared with DES [4–6]. Utilizing a DCB-based PCI strategy reduces the potential for stent-associated maladaptive biological responses in lesions treated without a permanent implant, thereby reducing total metal burden and facilitating vascular healing.

An observational, propensity-matched analysis comparing the management of single de novo diffuse lesions (≥30 mm) included patients treated with DCB-based PCI (DCB alone or in combination with DES), and those treated with DES alone. At the 2-year follow-up, DCB-based PCI was associated with a significant reduction in major adverse cardiac events compared with DES-only PCI (4.6% vs. 14.6%, $P < 0.001$; TVR: 3.1% vs. 9.7%, $P < 0.001$) [7]. Recently, Shin et al. reported that DCB-based PCI significantly reduced stent burden in multivessel PCI and led to a lower rate of major adverse cardiac events than DES-only treatment [8]. In the DCB-based group, 34.3% of patients were treated with DCB-only and 65.7% were treated with the DES hybrid approach. The number of stents and total stent length were significantly reduced by 65.4% and 63.7%, respectively, in the DCB-based group compared with the DES-only group. Moreover, the DCB-based group had a lower rate of major adverse cardiac events than the DES-only group (3.9% and 11.0%; $P = 0.002$) at the 2-year fol-

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low-up. The DES-only group was associated with a higher risk of cardiac death and major bleeding. These observational data suggest that a DCB-based PCI approach can reduce stent burden in multivessel CAD and may improve long-term outcomes by reducing late stent-related events (Table 15.1).

Together, these findings suggest that the use of DCB alone or in a DCB-DES hybrid strategy could serve as an alternative to DES-only treatment for selected patients with multivessel disease. DCBs can be used alone for smaller coronary vessels or in combination with DES for larger proximal lesions. Nonetheless, randomized studies and longer-term follow-up are needed for a more comprehensive assessment of the role of DCB treatment and its long-term clinical effects in this context.

Table 15.1 Comparison of two percutaneous coronary intervention strategies for patients with multiple lesions requiring revascularization

	DCB-based/ hybrid strategy	DES-only strategy
Stent metal burden (number or total length)	↓	Reference
Use of small-diameter DES	↓	Reference
Stent-related thrombotic risk	Potentially ↓	Reference
Bleeding risk	Potentially ↓ Observed ↓ in registries	Reference
Dual antiplatelet therapy duration	DCB-only stable de novo: ↓ DES implanted/ ACS: →	Reference
Complete revascularization feasibility	Potentially ↑	Reference

Arrows indicate mechanistic expectations and observational trends rather than definitive randomized evidence. DAPT duration should be individualized according to clinical presentation, bleeding and ischemic risk, and whether DES is implanted

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Dissection Left After DCB Angioplasty: Ally or Foe?

16

Verdiana Galli, Simone Fezzi, and Bernardo Cortese

Abbreviations

BRS	Bioresorbable scaffold
DCB	Drug-coated balloon
DES	Drug-eluting stent
FFR	Fractional flow reserve
iFR	Instantaneous wave-free ratio
LAD	Left anterior descending artery
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
QFR	Angiography-derived or Murray law-based quantitative flow ratio
RCA	Right coronary artery
TIMI	Thrombolysis in myocardial infarction

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16.1 Introduction

The use of drug-coated balloons (DCBs) for the treatment of coronary artery disease, by avoiding the permanent implantation of metallic scaffolds and embracing a true "leave nothing behind" strategy, has emerged as one of the most actively debated and rapidly evolving topics in contemporary interventional cardiology [1, 2]. Unlike conventional balloon angioplasty, the primary objective of DCB therapy is not merely mechanical lumen enlargement, but the homogeneous delivery of an antiproliferative drug into the vessel wall to prevent restenosis. For this reason, optimal lesion preparation represents a cornerstone of any successful DCB strategy [3]. Adequate plaque modification and vessel preparation are essential to minimize acute recoil, chronic negative remodeling, and neointimal hyperplasia, mechanisms that historically limited the efficacy of plain-old balloon angioplasty (POBA) [4, 5]. Although optimal lesion preparation is a key determinant of success also for drug-eluting stents (DES), the permanent mechanical radial strength of DES may partially compensate for suboptimal preparation, an option that is not available with DCB-based strategies. When DCB-based percutaneous coronary intervention (PCI) is planned, lesion preparation often requires a more aggressive approach, frequently involving specialty balloons, plaque-modifying or debulking devices, and high-pressure inflations to achieve adequate lumen expansion and ensure

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effective drug uptake. Such an approach, however, inevitably increases the incidence of angiographically-evident arterial dissections. Indeed, when assessed with high-resolution intracoronary imaging such as optical coherence tomography, some degree of vessel wall dehiscence can be identified in nearly all cases [6]. In the presence of flow-limiting dissections, bailout stenting, after prolonged balloon inflation or attempted fenestration, remains the recommended strategy. Conversely, non-flow-limiting dissections are often left untreated.

Early experience with DCB in peripheral arterial disease demonstrated favorable vascular healing, with progressive resolution of dissections and a tendency toward positive vessel remodeling over time [7]. Whether these observations can be fully extrapolated to the coronary circulation remains uncertain. In the DCB era, the evaluation of post-angioplasty dissections has shifted from purely anatomical classifications to a functional, flow-driven approach, with contemporary consensus documents identifying impaired coronary flow as the primary indication for bailout stenting [8, 9].

However, while angiographic criteria are relatively standardized, the introduction of intracoronary imaging has unveiled a higher burden of vessel wall injury, for which clear prognostic thresholds and treatment recommendations are still lacking. Consequently, imaging-guided management of coronary dissections remains heterogeneous and largely dependent on operator interpretation [1, 3, 10].

This chapter aims to review the current evidence on post-angioplasty dissection in the DCB era, methods of evaluations and mid-to-long-term outcomes.

16.2 Coronary Dissections During PCI: Historical Classification

Coronary artery dissections following POBA have traditionally been classified according to the National Heart, Lung, and Blood Institute (NHLBI) scheme, which is based on angiographic appearance and its theoretical impact on coronary flow. According to this classification, dissections are graded from type A to type F, reflecting increasing severity.

Briefly, types A and B represent mild dissections. Type A is characterized by a minor intraluminal radiolucency observed during contrast injection, with complete resolution after dye clearance. Type B presents as a double lumen separated by a radiolucent area, again without persistence of contrast. Type C corresponds to a moderate dissection, defined by limited but persistent contrast staining outside the lumen. Types D, E, and F represent severe dissections and are characterized, respectively, by spiral luminal filling defects; new persistent intraluminal filling defects associated with delayed antegrade flow; and impaired coronary flow or complete vessel occlusion [11, 12].

From a clinical standpoint, flow-limiting dissections, defined by a reduction in Thrombolysis in Myocardial Infarction (TIMI) flow to <3 and/or the presence of clinical or electrocardiographic signs of myocardial ischemia, represent a clear indication for bailout stenting to prevent acute vessel closure and ensure prompt restoration of coronary flow [7, 11–13]. Conversely, mild, non-flow-limiting dissections should not prompt stent implantation, as they have not been shown to adversely affect clinical outcomes [14].

Despite the widespread use of the NHLBI classification, the relationship between angiographic dissection type, spontaneous sealing, and the risk of subsequent restenosis remains incompletely understood, as does the functional impact of dissections on coronary physiology. This issue was first systematically explored by Albertal and colleagues, who investigated the effect of post-angioplasty dissections on coronary flow velocity (CFV) and their healing at six-month follow-up. Moderate dissections (type C) were associated with a transient reduction in coronary flow velocity reserve compared with mild or absent dissections (2.16 ± 0.60 vs. 2.82 ± 1.00 and 2.71 ± 0.88, respectively; $p < 0.05$). Proposed mechanisms

included delayed recovery of autoregulation, cholesterol embolization, and post-occlusive hyperemia. Although patients with moderate dissections experienced worse short-term outcomes, with a higher recurrence of angina at 30 days, no differences in CFV or major clinical events were observed at 6 months [15].

Recognizing the limitations of the NHLBI classification, Shigeyama and colleagues proposed an alternative angiographic classification for non-flow-limiting dissections (corresponding to NHLBI types B–D). This system incorporates two key morphological parameters: (1) the width of the dissection lumen relative to the reference vessel diameter (RVD), and (2) the depth of the dissection, defined by the extension of its outer edge beyond the true vessel lumen [12].

Using such criteria, dissections were categorized as follows: type A, superficial dissections confined to the vessel wall with a width exceeding one-quarter of the RVD; type B, dissections of similar width but with an outer edge extending beyond the reference lumen boundary; type C, small, confined linear dissections with a width <1/4 of the RVD; type D, narrow dissections (<1/4 of RVD) with deeper extension beyond the vessel boundary; and type E, protruding intimal flaps or spiral dissections, potentially flow-limiting and associated with a higher risk of restenosis. At 6 months, the highest rate of net luminal gain >0.3 mm was observed in type C dissections (41% vs. <20% in the other groups; $p < 0.001$), with no cases of restenosis reported in this subgroup. In addition, a larger reference vessel diameter was independently associated with a higher likelihood of dissection healing.

More recently, a new classification was proposed by Gitto and colleagues, who recommended stenting dissections in case of: (1) TIMI flow impairment (defined as TIMI <3); (2) persistent staining of contrast in the false lumen (>30 s); or (3) relevant vessel narrowing [10].

16.3 Prevalence of Dissections in Coronary Interventions

Vessel dissections during lesion preparation are a common consequence of barotrauma to the coronary vessel wall and, at a microscopic level, occur in nearly all cases. However, the reported prevalence of dissections varies widely across studies, largely depending on the definition applied and the method used for their detection. During the POBA era, the DEBATE II trial documented angiographically visible dissections in 73.4% of cases, with one-third being severe and requiring bailout stenting, while the remaining dissections were moderate and left untreated [15]. When assessed by conventional coronary angiography, dissections after DCB are reported in approximately 20–30% of cases in contemporary clinical trials when adjudicated by an independent core laboratory [6, 16–18]. In contrast, intracoronary imaging reveals intimal dehiscence from the underlying media in the vast majority of treated segments, with prevalence rates approaching 97%, compared with only 17% detected by angiography in the TRANSFORM I trial [6].

Overall, mild to moderate dissections (NHLBI types A–C) represent the most frequently observed patterns, whereas severe dissections (types D–F) are relatively uncommon, and the need for bailout stenting is limited to fewer than 10% of cases [4, 10, 12, 14, 19]. Importantly, in de novo coronary lesions treated with DCB, the rate of intentional crossover to DES has progressively declined over time, reflecting both a learning curve in lesion preparation and an improved operator understanding of the clinical relevance of post-angioplasty dissections and the true need for bailout stenting. Whereas early randomized trials reported crossover rates as high as 36% in PICCOLETO and 20% in BELLO [20, 21], more recent randomized studies consistently document rates in the range of 5–6%, underscoring the maturation of DCB technology and technique, as shown in Fig. 16.1 [18, 20, 22–25].

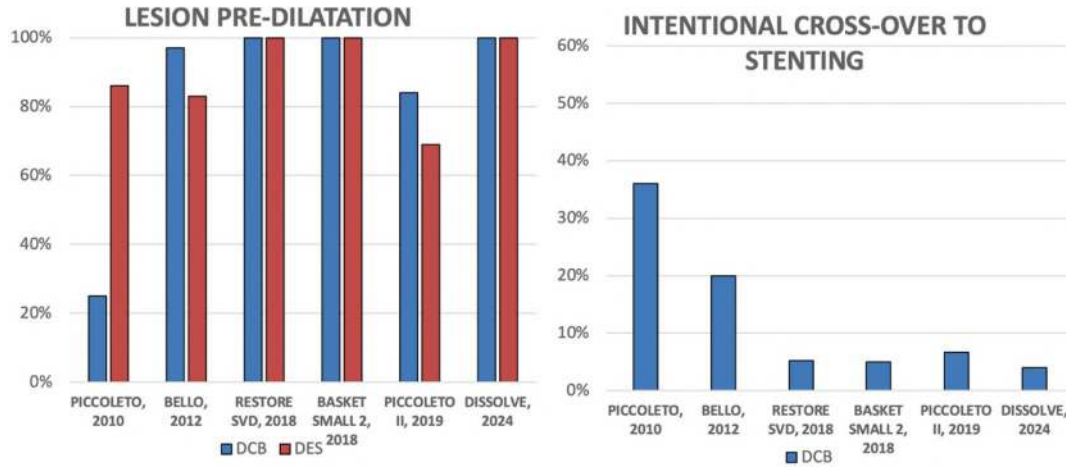


Fig. 16.1 Lesion preparation rate, and need for bailout stenting in different DCB trials. DCB drug-coated balloon, DES drug-eluting stent, SVD small-vessel disease

16.4 Causes and Mechanisms of Iatrogenic Coronary Dissections

The mechanisms underlying iatrogenic coronary dissections are complex and not fully elucidated. Early experimental and histopathological studies suggested that aggressive mechanical injury to the vessel wall could trigger an exaggerated intimal proliferative response [5]. In this context, Hermans and colleagues hypothesized that deep vessel wall injury might promote restenosis through enhanced smooth muscle cell proliferation, as observed in histopathologic specimens following balloon angioplasty [26, 27]. Subsequent studies supported this hypothesis, reporting higher restenosis rates in dissected vessels and proposing that intimal tearing could facilitate platelet adhesion and activation, ultimately leading to mural thrombosis [28]. Conversely, other investigations challenged this paradigm, suggesting that coronary dissections may be biologically neutral, or even potentially beneficial, by facilitating plaque fracture and vessel expansion, and failed to demonstrate a consistent association between dissection occurrence and restenosis risk [13, 27]. These divergent findings underscored the multifactorial nature of dissections and the difficulty in disentangling their mechanical, biological, and clinical consequences.

Insight into the anatomical and procedural determinants of coronary dissections was first provided by analyses from the Multicenter European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR). In this study, dissections were more frequently observed in the presence of higher residual diameter stenosis after angioplasty (>37%), eccentric and curved lesions, likely reflecting an unequal distribution of shear stress and vessel stretch during balloon inflation, intermediate lesion length (5–6.7 mm), right coronary artery involvement (possibly related to vessel curvature), angiographic thrombus, and balloon inflations at either low (<7 atm) or high (>9 atm) pressures, as well as with the use of non-compliant balloons [26].

Moreover, larger predilation balloon diameters, higher balloon-to–reference vessel diameter (RVD) ratios, larger DCB diameters, and higher DCB-to-RVD ratios have all been consistently associated with an increased risk of dissections [4].

Beyond procedural and technical aspects, lesion- and patient-related characteristics also play a significant role. In a retrospective study by Hui and colleagues evaluating DCB-only PCI, non-flow-limiting dissections were more frequently observed in lesions located in the left anterior descending artery (LAD), a finding sub-

sequently confirmed by other investigators [4, 10, 29]. This association may be explained by the anatomical features of the LAD, which is often tortuous, diffusely diseased, involves multiple side branches, and contains fixed bend points, factors that may increase susceptibility to vessel wall injury during balloon inflation [10].

Lesion length and baseline lesion severity have also been repeatedly implicated. At multivariate analysis, independent predictors of dissection included female sex (odds ratio [OR] 2.69, 95% CI 1.29–5.73; $p = 0.009$), stable coronary artery disease (OR 5.17, 95% CI 1.82–17.34; $p = 0.004$), lesion length (OR 1.11 per mm, 95% CI 1.04–1.18; $p = 0.001$), and higher DCB-to-RVD ratio per 0.1 increment (OR 1.36, 95% CI 1.06–1.79; $p = 0.020$), the latter emerging as the strongest predictor [4].

Vessel size has shown inconsistent associations across studies. In a single-center analysis by Yu et al., dissections occurred more frequently in small vessels (RVD <2.8 mm) than in larger vessels (35.7% vs. 28.3%; $p = 0.04$). Patients with small vessels were older, more frequently diabetic, and more likely to have calcified, complex (B2/C) lesions [19, 30]. In contrast, the retrospective study by Gitto et al. reported a higher prevalence of dissections in large vessels (RVD ≥3.0 mm), which may be more prone to acute recoil and vessel wall disruption due to a higher content of smooth muscle fibers. Although vessel size did not remain an independent predictor at multivariate analysis, lesion length >40 mm was associated with an increased risk of type C–E dissections (OR 3.47, 95% CI 1.33–9.03; $p = 0.011$) and bailout stenting (OR 2.62, 95% CI 1.22–5.64; $p = 0.014$) [10].

Additional lesion-related factors associated with an increased risk of dissections include moderate-to-severe calcification and the use of larger balloon diameters during both lesion preparation and DCB inflation [29]. In a single-center study involving 259 patients, the use of scoring balloons for lesion preparation prior to DCB inflation was associated with a significantly lower incidence of severe dissections (type C or higher) compared with semi-compliant or non-compliant balloons alone (9.8% vs. 31.8%; $p = 0.001$). At multivariate analysis, scoring balloon use independently predicted a lower risk of severe dissections (OR 0.18, 95% CI 0.05–0.49; $p = 0.002$) and a higher likelihood of achieving an optimal angiographic result (OR 3.08, 95% CI 1.47–6.58; $p = 0.003$) [31].

16.5 Outcomes of Dissections Following DCB Angioplasty in Peripheral Vessels

Early evidence on outcomes of dissections after DCB angioplasty comes from the peripheral vascular district, where DCB are often preferred over stents, which use is discouraged for the risk of fracture and restenosis due to limb movement [32, 33].

In the Taxan High-concentration UNcovered Delivery with Endovascular Release (THUNDER) study, despite similar rates of post-percutaneous transluminal angioplasty (PTA) dissections between paclitaxel-coated balloons (PCB) and uncoated balloons, PCB achieved better results: lower late lumen loss at 6 months (including in severe non-flow-limiting dissections ≥ type C), lower restenosis rates, and fewer target lesion revascularizations (TLR) at 2 years than the control group [34].

Conversely, a retrospective analysis showed that untreated severe dissections (types C–F) were associated with lower 2-year patency and higher TLR compared with lesions without dissection or with mild dissections (types A–B) [35].

In the AcoArt I (Prospective, Multicenter and Randomized Controlled Clinical Study to Verify Effectiveness and Safety of Drug-eluting Balloon in PTA Procedure) post-hoc analysis (5-year follow-up), clinically driven TLR was numerically lower with PCB versus PTA alone and the time free from TLR was longer, while mortality did not differ either between treatment strategies or between patients with and without dissections [7].

Spiral dissections, usually considered at high risk of acute closure, have been associated with worse outcomes even in case of preserved post-

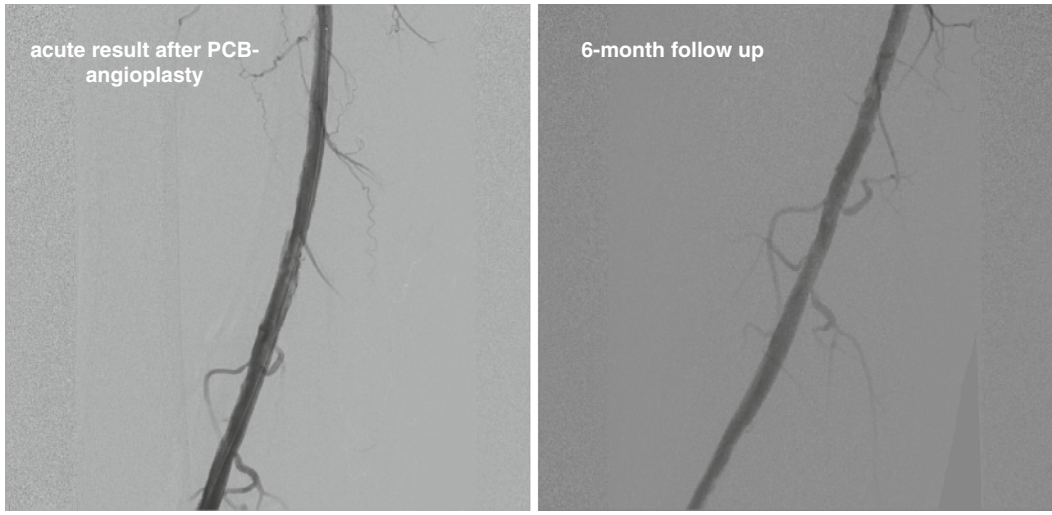


Fig. 16.2 Dissection left and healing after paclitaxel DCB angioplasty in the superficial femoral artery

PTA flow, with higher residual restenosis, increased restenosis rates and reduced freedom from TLR, and more major adverse events at follow-up [36] (Fig. 16.2).

16.6 Outcomes of Coronary Dissection Following DCB-PCI

Management of post-PCI coronary dissections has historically relied on the NHLBI classification, an approach derived from the POBA era that linked angiographic dissection severity to thrombotic risk and poor healing [29, 37].

In fact, the barotrauma induced by POBA triggers a long-lasting inflammatory and proliferative reaction that peaks at 3–4 months, without further worsening of the process beyond that time. Histological findings from deceased patients with evidence of restenosis showed exaggerated neointimal growth and proliferation encapsulating the dissected area within the intima. It derives that, the more the trauma, the more the risk of restenosis. Therefore, achieving higher acute luminal gain unavoidably pays the expenses of an increased late luminal loss, with a demonstrated linear correlation and an estimated 0.62 mm of luminal loss for each 1 mm of acute gain [5, 38].

More recent evidence suggests that DCB may substantially modify the natural history of post-angioplasty dissections, favoring vessel healing and positive remodeling. Intimal fracures induced by POBA create a space through dehiscence of the intima that expose vessel layers to the action of drug released by DCB [5]. Observational data consistently indicate that non-flow-limiting dissections following DCB-PCI are associated with a favorable clinical course, with short- and mid-term outcomes comparable to those observed in vessels treated with DCB without dissections [10, 14, 29]. Complete vessel healing seems to occur in most patients, with reported rates >90% at mid-term follow-up [4, 19, 29] (Fig. 16.3).

Type C dissections left untreated still raise concern and debate on their management. A substudy of the Doppler endpoints balloon angioplasty trial Europe (DEBATE) II investigated whether uncomplicated type C dissections after PCI impair coronary flow and whether additional stenting improves outcomes. After balloons angioplasty, patients were classified in two groups depending on the presence or absence of uncomplicated type C dissections (group A, $n = 45$ and group B, $n = 211$, respectively) and randomized to additional stenting or no further treatment. At 1 year, MACE and TLR were significantly higher in group A than group B (22% vs 11%, $p = 0.041$ and 17% vs 7%, $p = 0.016$).

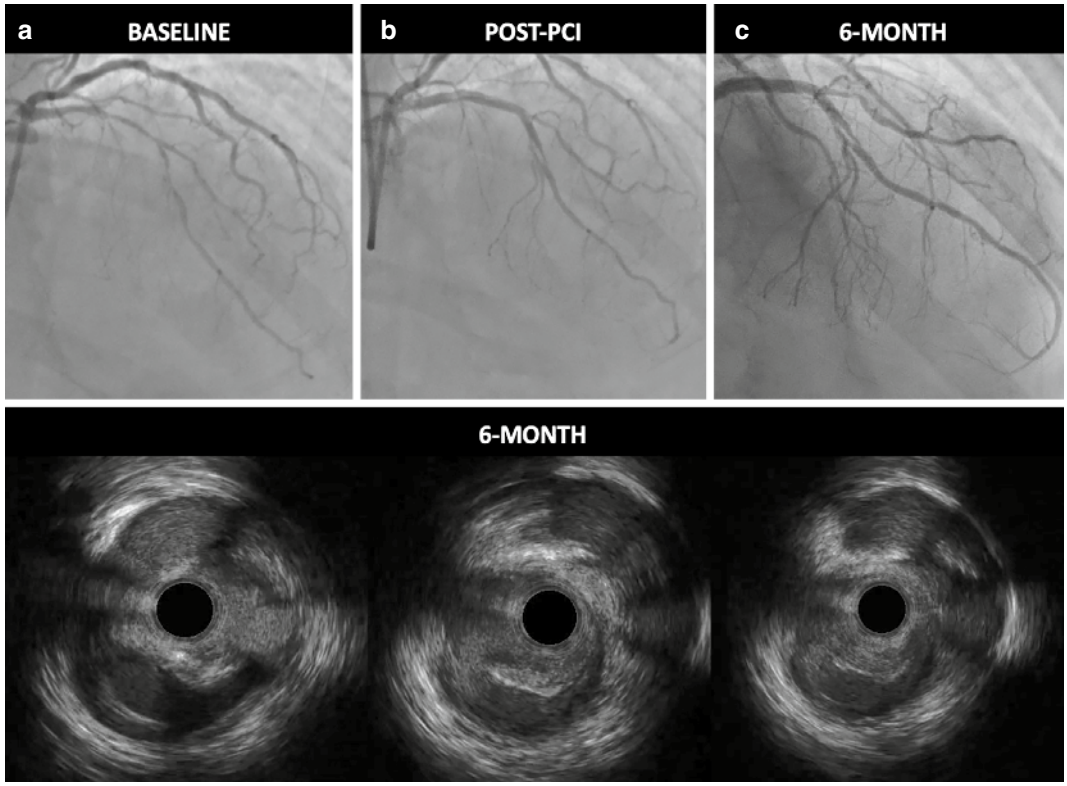


Fig. 16.3 67-year old patient, admitted for angina. Coronary angiogram showed multivessel disease with a long, diffuse disease of the LAD (**a**). Semi- and non-compliant balloons were used for lesion preparation prior to DCB inflation (2.5 × 40 mm). For acute recoil and dissection, a DES (3.0 × 26 mm) was implanted in the proximal segment. Residual distal dissection was left untreated, since the preserved flow and the absence of signs of ongoing ischemia (**b**). Three months later, the patient underwent RCA-staged PTCA. LAD angiogram showed the persistence of the dissection line, with a preserved TIMI3 flow (**c**). Conservative management was opted for

However, these findings were related to worse outcomes in patients who underwent stenting, with no significative difference between the two subgroups of non-stented lesions (MACE: 31% vs 6%, $p = 0.002$ in stented A and B subgroups; 19% vs 16%, $p = ns$ in the non-stented A and B subgroups; TLR: 31.3% vs 3%, $p < 0.001$ and 13% vs 11%, $p = ns$ in stented versus non-stented groups, respectively). Stratifying moderate dissections by coronary flow reserve impairment after angioplasty did not meaningfully change the long-term risk. The authors discuss a plausible mechanism whereby adding a stent to an injured vessel wall could amplify inflammation and blunt "favorable remodeling," offsetting any scaffolding benefit. In conclusion, routine additional stenting in moderate uncomplicated dissections, where TIMI 3 flow is maintained and no signs of ischemia emerge, does not improve—and may worsen—clinical outcomes [11].

In an observational study including 466 patients (522 lesions) with de novo coronary lesions (including both small and large vessels), in which intention-to-DCB PCI was planned and performed, comparable two-year clinical outcomes between dissected vessels left untreated—in the absence of impaired TIMI flow, persistent contrast staining in the false lumen, or acute recoil—and vessels without dissections, were reported. Specifically, the cumulative incidence of target lesion failure did not differ significantly between groups (2.7% vs. 4.2%; log-rank $p = 0.324$). As expected, the need for bailout

stenting increased progressively with dissection severity [10].

Consistent findings have been reported across multiple studies, showing favorable outcomes for non-flow-limiting dissections after DCB-PCI. Overall, rates of target vessel revascularization (TVR) and target vessel failure (TVF) at short- and mid-term follow-up are generally below 10%, while bailout stenting during the index procedure is required in approximately 5–15% of de novo lesions [10, 29, 39–41] (Figs. 16.4 and 16.5).

From a mechanistic perspective, non-flow-limiting dissections in DCB-PCI have been associated with greater acute lumen gain compared with lesions without dissections and with the phenomenon of late lumen enlargement (LLE) [1, 29, 31, 42, 43]. One proposed explanation is that the creation of an intimal tear may facilitate deeper and more homogeneous drug penetration into the vessel wall, enhancing the antiproliferative effect of the coating. However, the precise mechanisms underlying dissection healing, the determinants of positive remodeling, and the potential differential effects of various antiproliferative agents remain incompletely understood [44]. Notably, an observational study by Cortese and colleagues did not identify a clear relationship between dissection type or severity and the propensity for healing [29].

Although the exact biological pathways governing dissection healing and positive vessel remodeling after DCB-PCI are not fully elucidated, it is reasonable to assume that the antiproliferative drug plays a central role by suppressing smooth muscle cell proliferation and facilitating sealing of vessel wall disruptions, particularly with newer-generation, highly efficient DCB. Improvements in adjunctive pharmacotherapy, including the widespread use of more potent antiplatelet agents, may further contribute to favorable healing responses [29]. Notably, high rates of dissection sealing have also been reported with very short dual-antiplatelet therapy (DAPT), suggesting that effective drug delivery to the vessel wall, rather than prolonged antithrombotic therapy, may be the dominant determinant of healing in this setting [29].

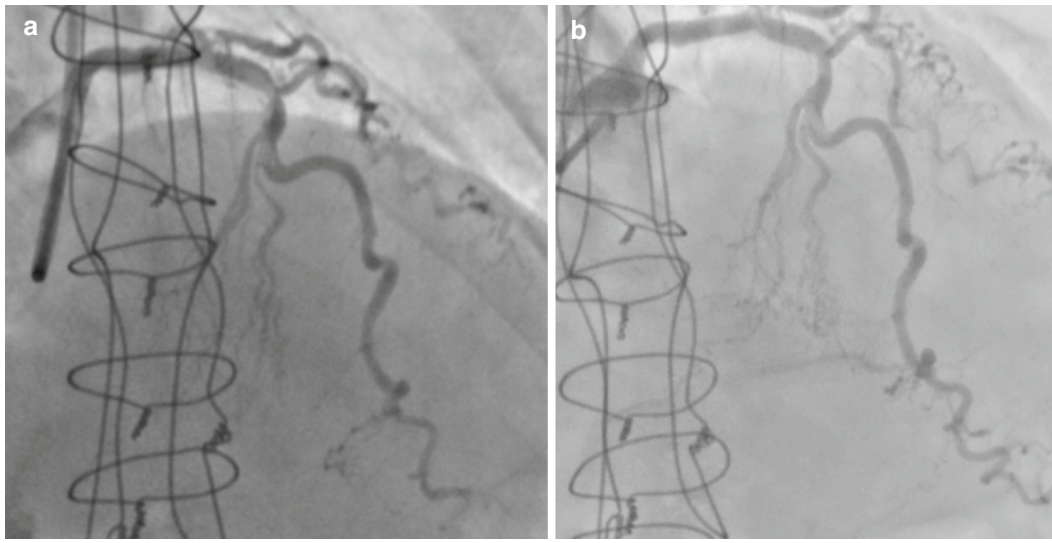


Fig. 16.4 75-years old patient with a history of prior surgical revascularization (2016), left main stenting (2018) and DCB-PCI on the LAD (2022), with residual non-flow-limiting dissection, that was left untreated (**a**). In January 2026, a coronary angiogram was repeated for suspected angina. LAD angiogram showed a chronicized dissection with persistence of haziness, with preserved flow (**b**). The patient was medically managed

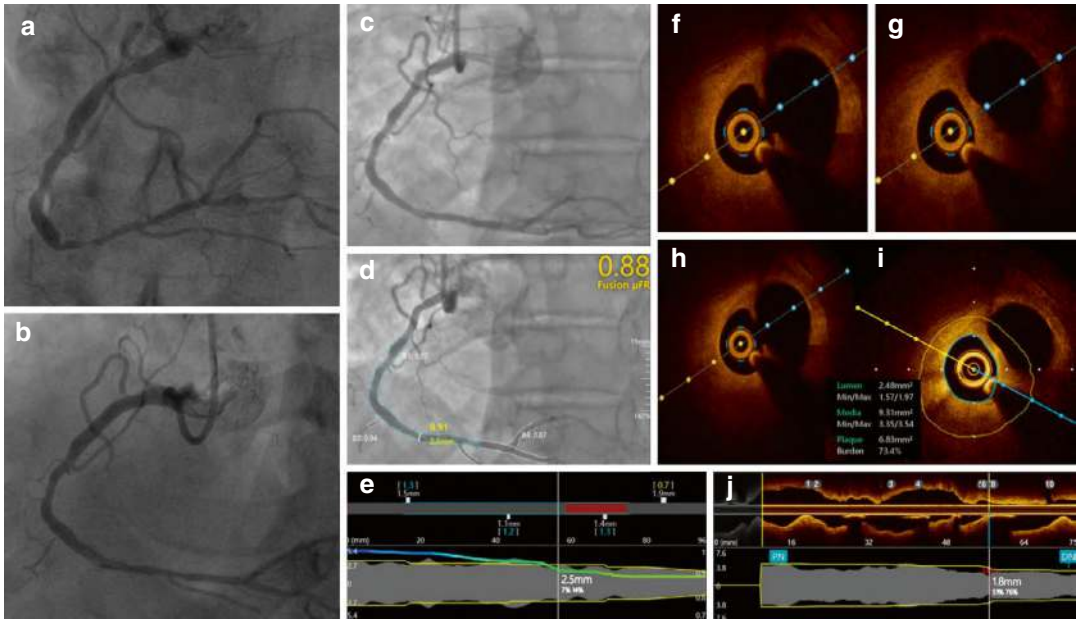


Fig. 16.5 Type B dissection after DCB-PCI of the distal RCA (**a**, **b**). After 6 months, an angiogram was repeated, showing a nearly complete healing of the dissection with residual mild haziness (**c**). The angio-derived index of flow reserve (µFR) excluded its functional relevance (**d**) and the pullback curve showed no relevant pressure drop (**e**). OCT showed a recanalized dissection with double-lumen appearance (**f–l**): the true and false lumen were separated by a dissection flap and some fenestrations (entry/re-entry sites) were visible. Luminal area was deemed acceptable

16.7 Dissections Healing: Are All the DCB Equally Effective?

It is well established that DCB do not exhibit a class effect. Key determinants including drug formulation, crystal morphology, excipients and coating technologies, as well as the kinetics of drug retention and penetration into the vessel wall, are device specific. Consequently, the impact of different DCB platforms on positive vessel remodeling and dissection healing varies substantially [1].

The two main antiproliferative drugs, paclitaxel and sirolimus, present markedly different pharmacokinetics properties and protein targets, which dictate their distribution profiles and biological effects.

Paclitaxel irreversibly binds polymerized microtubules, inhibiting vascular smooth muscle cells (VSMCs) mitosis, with drug anchoring mainly in the subintimal space and a steep gradient toward the adventitia. Its high lipophilicity allows rapid cellular uptake and sustained, relatively homogeneous delivery to VSMCs [2, 14]. Sirolimus, instead, binds a cytosolic protein and arrests the cell cycle in G1 phase; it distributes more uniformly across media and adventitia but transfers less efficiently because of higher hydrophilicity, potentially leading to more heterogeneous tissue absorption and retention [45, 46]. New delivery technologies aim to improve -limus DCB pharmacokinetics and achieve more controlled, sustained release. It remains uncertain whether these formulations can match paclitaxel's tissue uptake and retention [1, 47, 48]. Excipients themselves can also affect vessel wall adhesion and deposition of the same drug [49].

Although no specific studies have compared outcomes of dissections in DCB-PCI using different platforms, some preliminary data are emerging.

For instance, positive vessel remodeling with late lumen increase has been observed in nearly

two-thirds of cases following PCB-PCI, compared with about one-third of cases using sirolimus-coated ballons (SCB) [1]. Recently, Ninomyia and colleagues observed that first-generation SCB MagicTouch (Concept Medical, Tampa, Florida, USA) resulted in a significantly higher LLL at 6 months and less LLE compared with PCB (SeQuent Please Neo, B.Braun, Melsungen, Germany) in the treatment of de novo small-vessel disease [50]. With an LLL of 0.00 mm (±0.32) versus 0.32 mm (±0.47) ($p < 0.001$), and an LLE observed in 53.7% and 30.0% of lesions in the PCB and SCB groups, respectively (odds ratio [OR] 2.60, 95% CI 1.36–9.44, $p = 0.012$), SCB failed to demonstrate the non-inferiority in terms of angiographic net lumen gain at 6 months. Optical coherence tomography (OCT) analysis revealed that dissection volume correlated with LLL in the SCB group but not in the PCB group, probably suggesting a suboptimal and insufficient antiproliferative effect of SCBs under barotrauma. Clinical events and revascularization procedures at follow-up were rare and occurred at similar rates between groups [50]. One of the arguments against this trial was the lack of a systematical lesion preparation protocol, which could have led to the final results under the assumption that paclitaxel is a more forgiving drug if the vessel is not prepared adequately [51]. This argument is also emphasized by the results of the PICCOLETO VI multicenter study, which showed a similar performance of SCB and PCB, after an adequate lesion preparation is achieved at expert centers, in terms of *late functional loss*, an index of difference between angiographic-derived physiological parameters between the end of PCI and angiographic follow-up [52] (Fig. 16.6).

A meta-analysis by Scheller et al. analyzing 26 randomized controlled trials and 4500 patients

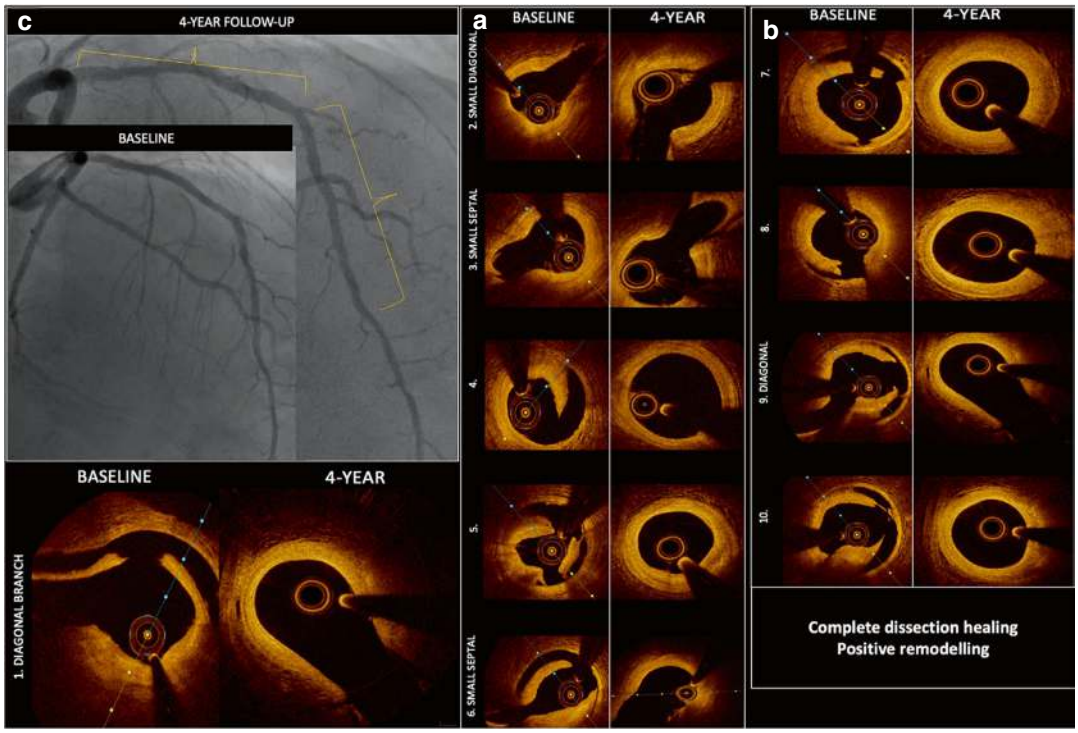


Fig. 16.6 Diffuse LAD disease with impaired coronary flow (QFR = 0.68, iFR = 0.73, FFR 0.71) and OCT-confirmed high plaque burden (**a**). Hybrid treatment with BRS and DCB angioplasty was performed restoring physiological parameters (QFR = 0.91, iFR = 0.96, FFR 0.94) and achieved optimal lumen expansion. Extensive dissection involving the media was confirmed at the OCT analysis after DCB treatment (**b**). Four-year follow-up showed complete dissection healing and positive vascular remodeling (**c**). Integration of QFR and OCT enables precise evaluation of residual ischemia and vessel healing, guiding tailored DCB-PCI strategies

reported favorable outcomes on mortality with the use of different DCB platforms. Iopromide platforms were predominantly used and the cohort using alternative excipients (i.e., urea, butyryl-tri-hexyl-citrate [BTHC], shellac-amonium salt) were smaller, limiting the possibility of comparisons or speculations on platform-specific outcomes.

Regarding the role of excipients in drug pharmacokinetic, observational data suggest similar outcomes with both iopromide-based and urea-based PCB. However, important limitations of these studies—mostly single-center, observational and involving patients of a single ethnicity—preclude extrapolation and robust comparison between different platforms [49, 51]. A recent report on a subanalysis of the EASTBOURNE study shows how leaving a dissection after SCB is safe and not associated with impaired clinical outcome after 1 year, with no differences with the cohort of lesions left without angiographic dissection [52].

In conclusion, convincing data on favorable outcomes of dissections after DCB-PCI are leading to a shift in their management. Some operators advocate the creation of "therapeutic" or "wanted" dissections as a crucial factor to secure lumen area. Selected cases with preserved flow and acceptable MLD do not carry an increased risk of adverse events at follow-up and additional stenting does not improve patients' outcomes [4, 11, 26]. On the other hand, "unwanted" severe dissections that may result in myocardial infarction or other complications clearly require additional angioplasty or stenting.

16.8 Coronary Physiology in Dissections Following DCB-PCI

Coronary physiology, based on either pressure-wire or angiography-derived indices, can help guide revascularization and in PCI optimization. Its role in DCB-PCI has never been specifically addressed, with available data mainly deriving from expert consensus and retrospective observational research. Given the peculiar processes following DCB use, including promotion of positive vessel remodeling and dissections healing, a potential improvement in physiological indices at follow-up may be expected, or at least hypothesized.

The DCB-ARC Consensus Group Report suggested the use of fractional flow reserve (FFR) with a threshold of 0.80 as an acceptable compromise after angioplasty to define adequate lesion preparation prior to DCB inflation [3]. The use of a Pd/Pa (distal pressure/aortic pressure) ratio ≥0.90 was proposed in the REDUCE STENT (dRug-coatED balloon angioplasty gUided by post-perCutanEouS coronary inTErvention pressure gradieNT) retrospective registry. Pursuing a DCB-PCI strategy when lesions had a Pd/Pa ≥ 0.90, TIMI 3 flow, residual stenosis <30%, and absence of dissections >type B, the authors reported a very low incidence of vessel occlusion at a median of 246 days (interquartile range [IQR] 136-400), suggesting the adoption of less stringent criterions in this setting, where prevention of vessel closure may take precedence over maximizing acute lumen gain [53, 54]. In the PICCOLETO VI study including 227 patients, post-PCI angio-based FFR was a strong predictor of ischemic physiology (≤0.80) at follow-up, showing good discriminative performance (AUC 0.758) regardless of DCB type. A post-DCB angio-based FFR cut-off ≤0.86 identified follow-up ischemia with high accuracy (81%) and an excellent negative predictive value (92%). In contrast, angiographic % diameter stenosis (≥30%) failed to predict follow-up ischemia and performed significantly worse than post-PCI physiology [55].

However, in the absence of robust evidence, no specific physiological indices or thresholds are currently recommended by the recent DCB Academic Research Consensus position paper [1].

16.9 Intracoronary Imaging for Dissections Evaluation

Data on intracoronary imaging in the context of DCB-PCI are scarce. Edges dissections after stent implantation can be assessed with OCT, with specific criteria of severity that

have been shown to predict both safety and efficacy outcomes [56]. Conversely, no specific imaging criteria exist for assessing the result of DCB-PCI or for grading dissections in this setting

A relevant discrepancy exists between the proportion of dissections detected by intravascular imaging and by angiography [5]. Indeed, minor dissections may be detectable only by high-resolution intravascular imaging technologies [57]. For instance, a recent case series on dissections in in-stent restenosis (ISR) reported that the OCT revealed dissections of neointimal tissue in all lesions, whereas these were not visible angiographically. At 6 months, OCT also showed a complete sealing of all dissections [42].

In a single-center experience, the decision whether to implant a stent or pursue a DCB strategy when a dissection was detected after lesion preparation was based on the presence of a residual lumen <50% of RDV (media-to-media), as measured by intravascular ultrasound (IVUS). Interestingly, IVUS use was associated with a lower risk of bailout stenting (OR 0.41, 95% CI 0.17–0.96) [10].

While strong evidence supports ICI use for and after stent implantation, limited data are available on its role following DCB-PCI. ICI provides detailed assessment of vessel size, plaque composition, extent, and morphology, allowing for more optimized lesion preparation compared with angiography alone. The DCB-ARC consensus recommends incorporating ICI to achieve precise vessel sizing, appropriate DCB selection, and better characterization of plaque morphology, all of which may lead to superior angiographic outcomes [2]. In the ULTIMATE III trial, IVUS-guided DCB angioplasty was compared with angiography guidance in 260 high-bleeding risk patients with de novo lesions. IVUS guidance resulted in greater acute lumen gain, lower late lumen loss (−0.10 ± 0.34 mm vs. 0.03 ± 0.52 mm; $p = 0.025$), and larger minimal lumen diameter with less residual stenosis at 7-month follow-up. Although the study was not powered for clinical outcomes and found no significant difference in target vessel failure, IVUS guidance provided superior angiographic results, supporting its potential role in optimizing DCB angioplasty [58].

In an OCT- and physiology-guided study including 50 de novo lesions, Yamamoto et al. observed that lesions with LLE at follow-up exhibited a lower post-procedural area stenosis after DCB angioplasty (38.8% vs. 52.2%; $p = 0.01$), highlighting the potential prognostic value of early anatomical results for subsequent positive vessel remodeling. Furthermore, intimal fractures with separation of the intima from the media are associated with improved outcomes after DCB-only PCI. The study also highlighted the importance of physiology and the timing for its re-assessment after DCB inflation, to detect potential recoil and dissection progression. In fact, lesions which showed an early decline of FFR and instantaneous wave-free ratio (iFR) 15 min post-PCI resulted in significantly lower LLE at follow-up. Finally, in the three cases requiring bailout stenting, medial dissection was visible [59]. The extent of dissection into deeper vessel layers may be a marker of a larger injury and potentially predispose to injury propagation, recoil and lumen compromise, especially in case of intramural hematoma, consequently leading to side-branch jeopardy, flow limitation and increased risk of vessel occlusion. Thus, medial dissection at ICI represents a “red flag” and attention must be paid to early detect potential signs of flow compromise.

Therefore, controlled dissections can be beneficial by facilitating vascular remodeling and enhancing drug penetration into the vessel wall. However, no evidence-based intravascular imaging criteria for DCB optimization have yet been established and according to a Japanese Clinical Expert Consensus medial dissection together with intramural hematoma or extra medial injury should be covered with ‘bail-out’ stenting [8].

These preliminary data should stimulate reflections on the impact of minor dissections, which often remain untreated because they are not visible angiographically, and do not appear to have clinical relevance. On the other hand, collection of more intracoronary imaging data is needed to better understand the physiopathological mechanisms and evolution of dissections.

16.10 Conclusions and Future Perspectives

The use of DCB in PCI may offer relevant advantages, especially in situations where DES implantation is expected to perform suboptimally. Drug transfer into the vessel wall reduces VSMC proliferation, slows neointimal growth and promotes positive vessel remodeling. Therefore, effective and homogeneous delivery of the antiproliferative drug to the vessel wall is crucial to the success of DCB. Whether the creation of intimal breaches may improve or further promote drug penetration into the vessel remains to be clearly demonstrated. Current data on dissections in the context of DCB-PCI suggest favorable effects when non-flow-limiting dissections are present, with promotion of positive vessel remodeling and late lumen enlargement at follow-up. Moreover, convincing data show that most of non-severe dissections (type A, B and some type C) tend to heal over time. However, these data mostly derive from observational studies, registries and retrospective analysis.

In addition, in light of these preliminary results, the need to redefine post-angioplasty dissections is emerging. The traditionally used NHLBI classification appears somewhat "limited" and incomplete to adequately describe and assess dissections in the era of DCB-PCI. Other important unmet needs are the physiological assessment of dissections and the development of intravascular imaging criteria to define their relevance and guide treatment decisions.

At present, management of dissections is often left to operators' discretion, with a probably higher propension not to treat uncomplicated dissections in high-expertise centers.

Future research focusing on the role of physiology and intracoronary imaging in the setting of DCB-PCI, as well as on a better understanding of drug effects within the vessel wall and healing mechanisms, is strongly advocated.

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17 Can Drug-Coated Balloons Exert Late Lumen Enlargement, and Is This Good?

Victor A. Jiménez Díaz and Rishi Puri

17.1 Introduction

DCBs have emerged as a vibrant technology in treating coronary and peripheral artery diseases, offering an alternative to stent-based approaches, with the premise of 'leave nothing behind' being notionally attractive for the lifetime management of coronary artery disease. Unlike drug-eluting stents (DES), DCBs deliver antiproliferative drugs directly to the vessel wall without leaving behind a permanent scaffold, making them ideal for small vessels, bifurcations, lesions prone to restenosis, and patients at high risk of bleeding. Vessel healing in the absence of a permanent or temporary scaffold promotes true vascular restoration [1–3] from a vessel structural and functional aspect [5–7].

One of the most intriguing outcomes observed with DCB is late lumen enlargement (LLE), a phenomenon where the treated vessel's lumen size increases over time (Figs. 17.1 and 17.2), rather than experiencing the typical restenosis seen with other interventions. LLE has raised interest in the interventional cardiology community due to its potential to enhance long-term lumen patency, possibly reduced restenosis rates which could translate into improved clinical outcomes. But its unpredictability raises questions about its consistency and the potential risks of over-expansion, such as late vessel instability, ectasia or aneurysm formation, in situ thrombosis and even vessel rupture in extreme circumstances.

17.2 Can Drug-Coated Balloons Exert Late Lumen Enlargement, and Is This Beneficial?

From the first case report of LLE [4–11] after DCB treatment [8] to the first initial finding in a series of patients with CAD [9], different studies have reported LLE after DCB treatment in the coronary arteries [10], peripheral arteries [11] and arteriovenous fistulas [12]. In the first mechanistic study conducted in two centers, a series of 58 cases with severe de novo CAD were retrospectively analyzed after DCB treatment with two different paclitaxel-based DCB (SeQuent Please from B. Braun, Melsungen, Germany, and In.Pact Falcon from Invatec-Medtronic, Italy) and angiographic follow-up were conducted 4 months after DCB-PCI. A

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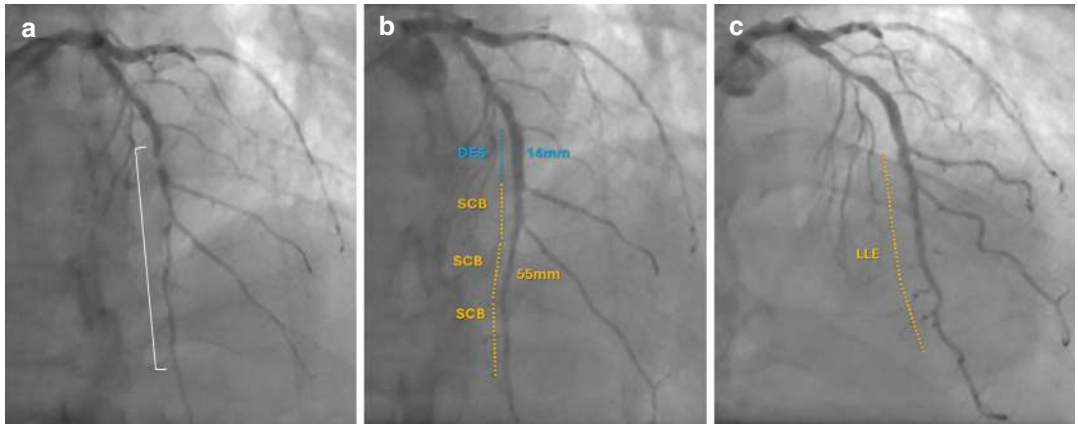


Fig. 17.1 Late lumen enlargement after a hybrid approach. Angiographic images show: (**a**) baseline left anterior descending (LAD) artery with diffuse, severe disease in the mid and distal segments (white bracket); (**b**) final result after hybrid PCI with one drug-eluting stent (blue dotted line) and three sirolimus-DCBs from the distal to the mid LAD (yellow dotted lines); and (**c**) 4-month follow-up demonstrating late lumen enlargement within the sirolimus-DCB–treated segments (yellow dotted lines)

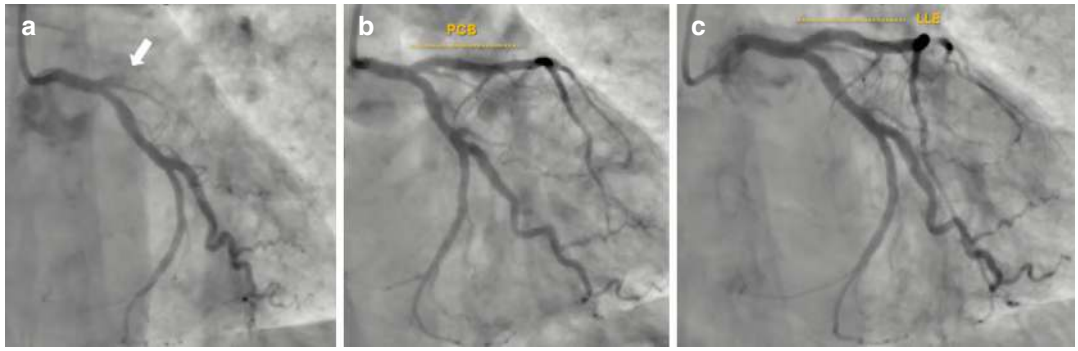


Fig. 17.2 Late lumen enlargement in a STEMI case treated with a paclitaxel-DCB–only PCI strategy. Angiographic images show: (**a**) baseline acute occlusion of the proximal left anterior descending (LAD) artery (white arrow); (**b**) final result after DCB-only PCI using a single paclitaxel-DCB (yellow dotted lines); and (**c**) 4-month follow-up demonstrating late lumen enlargement within the DCB-treated segment (yellow dotted lines)

total of 69% of patients showed luminal enlargement, whereas 29% had minor luminal loss [9].

Studies using IVUS showed that LLE occurred in 74% of patients initially treated with paclitaxel-DCB at 9-month follow-up. Also, most (86.0%) IVUS-derived dissections were healed. The non-flow limiting larger dissection just after DCB treatment may strongly be associated with subsequent LLE. The dissection index was the strongest predictor of the change in mean lumen volume [13]. LLE after DCB treatment may be caused by vessel enlargement and plaque regression [14]. This hypothesis is supported by findings from a 28-patient study of paclitaxel-DCB PCI evaluated with IVUS and fractional flow reserve (FFR) [15]. In this study, the mean vessel area and lumen area significantly increased after 9 months; mean plaque area remained unchanged, however percent atheroma volume decreased significantly; all four IVUS-VH plaque compositions were unchanged; and the functional patency with FFR was maintained during the 9 months follow-up.

However, the lack of standardization of the ideal time of follow-up angiography for LLE mea-

surement, as well as the lack of an independent core laboratory analysis casts some doubt on the generalizability of these data. In the current DCB era, in which both paclitaxel- and sirolimus-coated balloons are being actively evaluated, true serial IVUS assessment of the entire vessel wall would be particularly valuable to determine whether DCBs exert genuine anti-atherosclerotic effects and to better characterize their impact on both the lumen and vessel wall. This distinction is important because serial IVUS studies of the natural history of coronary atherosclerosis have established that positive or outward vessel remodeling may accompany increasing atheroma burden, while serial IVUS has also become an important tool for evaluating therapies targeting coronary atherosclerosis [12–15]. Therefore, positive remodeling after DCB treatment should not necessarily be interpreted as evidence of plaque regression or vascular restoration. Even if DCB-induced lumen enlargement proves to be unrelated to true plaque regression, a larger residual lumen may nevertheless carry prognostic relevance at the lesion level. The PROSPECT study demonstrated that future lesion-related events preferentially arose from segments characterized by greater plaque burden and smaller lumen areas [16, 17]. Thus, achieving a larger lumen after DCB treatment could potentially be beneficial independently of changes in plaque composition or stability.

17.3 Mechanism of Late Lumen Enlargement

LLE is thought to result from a combination of mechanical and biological processes. The drug (commonly paclitaxel, with nowadays sirolimus possibly entering commercial practice outside the US) delivered by the DCB inhibits smooth-muscle cell proliferation, reducing neointimal formation and thus preventing restenosis. Over time, it is hypothesized that positive vessel remodeling, facilitated by the absence of a permanent metallic scaffold may contribute to the observed lumen enlargement. Inflammatory responses and the resolution of early vessel wall injury may also promote this effect.

OCT analyses following paclitaxel- and sirolimus-coated balloon angioplasty for de novo coronary lesions have provided valuable insights into the mechanisms underlying LLE. These studies demonstrated that the increase in lumen area over time was primarily driven by vessel enlargement, healing of procedural dissections, and regression or resorption of plaque tissue [18, 19].

The observed lumen enlargement is thought to be primarily related to the cytotoxic effects of paclitaxel on the vascular wall, leading to medial thinning and vessel expansion. This mechanism appears more likely to occur following paclitaxel-coated balloon treatment than with sirolimus-based technologies, in which antiproliferative effects are achieved through different, non-cytotoxic pathways [18, 19]. By local drug release to the vascular wall, positive effects to reduce neointimal hyperplasia and even to increase vascular lumen are possible. Paclitaxel leads to inhibition of smooth muscle cell (SMC) proliferation by modulation of the microtubule formation and upregulation of proapoptotic factors [20]. Initially, it is found in a much higher concentration in the vascular wall after DCB use than after DES implantation [21, 22] leading not only to cytostasis but also to mitotic and post-mitotic arrest [23]. Dissections can help transmural diffusion of the drug and enable paclitaxel to be delivered in high doses near the adventitia. Thus, it is conceivable that more profound effects not only on neointimal growth but also on medial thinning and enlargement are caused by paclitaxel. Greater reductions of SMC content in the intima and media after DES implantations while using similar doses of paclitaxel and sirolimus has been previously described [20]. Since the most pronounced lumen enlargement was seen in the area with the highest plaque burden of the treated segment, plaque regression or vascular healing could be alternative explanations. This finding reveals the possibility that plaque regression may be another mechanism leading to LLE (late positive vessel remodeling). A previous study demonstrated that circumferential deep vessel wall injury is correlated with late vessel size [24] and another study showed that medial dissection with intimal disruption is a possible mechanism of LLE [25].

17.4 Clinical Evidence of Late Lumen Enlargement

Several studies have reported LLE in patients treated with DCB, particularly in small vessel disease [10, 13, 26–30]. Data from trials have shown that, in some cases, the lumen size not only remains stable but actually increases over time, often between 3 and 12 months post-procedure. This contrasts with DES, where the luminal diameter tends to plateau or slightly decrease due to neointimal growth (Table 17.1).

17.5 Is Late Lumen Enlargement Exclusive to Paclitaxel or Dependent on the Type of Drug?

LLE has been observed predominantly in studies involving paclitaxel-DCB, but the phenomenon is not necessarily exclusive to paclitaxel. The ability of a DCB to induce LLE likely depends on several factors, including the type of drug, the drug's release kinetics, the biological response it triggers, and the specific characteristics of the vessel or lesion being treated.

Why paclitaxel? Paclitaxel is known for its antiproliferative cytotoxic properties, which inhibit smooth-muscle cell proliferation and neointimal hyperplasia, two key drivers of restenosis. The drug's high lipophilicity allows for rapid uptake into the vessel wall with sustained efficacy, contributing to positive vessel remodeling in some cases. This has been associated with LLE, where the vessel's diameter increases over time rather than restenosing.

Research with sirolimus-coated balloons (SCBs) is emerging, but the data on LLE with sirolimus or other drugs is less established. Sirolimus is cytostatic (rather than cytotoxic), has a slower uptake and longer action time compared to paclitaxel, which could result in different vascular responses. So far, studies with sirolimus-coated balloons (SCBs) have focused mainly on reducing restenosis; unlike the larger paclitaxel-DCB literature, evidence quantifying LLE after SCB remains limited and heterogeneous. Yet, emerging small-vessel trials, observational cohorts, and intracoronary imaging substudies are beginning to show modest late lumen increases, influenced by DCB-only vs. bailout strategies and by device formulation (Table 17.2).

These studies show promising results after SCB angioplasty, with LLE reported in the range of 0.20–0.30 mm across various studies. The data is still less abundant compared to paclitaxel, and sirolimus exhibits slower drug uptake, which may affect its ability to induce LLE compared to paclitaxel. The follow-up period and patient populations (e.g., small-vessel disease, high-risk patients) influence the reported outcomes.

While paclitaxel is the dominant drug studied for LLE, SCB are showing encouraging results, but whether it can occur with other drugs like sirolimus or future antiproliferative agents requires further investigation. Understanding the mechanisms behind LLE with different drugs could have significant implications for selecting the most appropriate therapy in specific patient populations.

17.6 Is Late Lumen Enlargement Beneficial?

The clinical implications of LLE are still under investigation. On one hand, it may represent a favorable long-term outcome with respect to vessel/segment patency, whereas on the other hand it may also suggest that DCB can promote healing and expansive vessel remodeling in a way that is not possible with metallic stents. For patients with small vessels or those at high risk for restenosis, this effect could translate into better long-term outcomes, fewer repeat procedures, and reduced dual antiplatelet therapy duration.

On the contrary, excessive positive vessel remodeling could potentially lead to vessel wall weakening or ectasia/aneurysm formation in rare instances, with a reported incidence of 0.8% in non-chronic total occlusions (CTO) lesions after paclitaxel-DCB treatment, up [33] to 8.0% in CTO lesions [34]. Reported rates of coronary aneurysm formation after PCI vary by modality: around 3.9% after percutaneous transluminal

Table 17.1 Shows both randomized trials and observational studies reporting LLE in de novo CAD lesions treated with various paclitaxel-DCB technologies

Study	Study type	Drug	Late lumen loss (LLL)	% with LLE	Follow-up period	Patient population	Imaging modality for LLE
PEPCAD I	Prospective observational	Paclitaxel (PCB)	In-segment: 0.16 ± 0.38 mm	NR	6 months	De novo SVD	QCA
BELLO	Randomized trial	Paclitaxel (PCB) vs. Paclitaxel (DES)	In-segment: 0.05 ± 0.37 mm	NR	6 months	De novo SVD	QCA
PICCOLETO II [31]	Randomized trial	Paclitaxel (PCB) vs. Everolimus (DES)	In-segment: 0.01 ± 0.25 mm	NR	6 months	De novo SVD	QCA
Funatsu 2017 (Clin Res Cardiol)	Multicenter RCT	Paclitaxel (PCB) vs. POBA (uncoated balloon)	In-segment: 0.01 ± 0.31 mm	48.0%	6 months	De novo SVD	QCA
Ann 2016 (PLoS One)	Prospective observational	Paclitaxel (PCB)	In-segment: 0.02 ± 0.27 mm	NR	9 months	De novo CAD	QCA, Imaging (IVUS-VH), Physiology (FFR)
Yamamoto 2024 (EuroIntervention)	Retrospective observational	Paclitaxel (PCB)	In-segment: 0.01 ± 0.37 mm	40.7%	6 months	De novo CAD	QCA, Imaging OFDI (OCT)
TRANSFORM I—Ninomiya (JACC Intv)	Multicenter RCT	Sirolimus (SCB) vs. Paclitaxel (PCB)	In-segment: 0.01 ± 0.31 mm	53.7%	6 months	De novo SVD	QCA (OCT-guided sizing)
Yamada 2023 (J Cardiol)—Elective DCB vs. DES (unrestrictive de novo lesions)	Retrospective observational	Paclitaxel (PCB)	In-segment: 0.07 ± 0.45 mm	45.3%	11 months	De novo CAD	QCA
Lu 2019 (J Cardiol)—DCB-only in large vessels	Prospective observational	Paclitaxel (PCB)	In-segment: 0.02 ± 0.49 mm	61.5%	9 months	De novo large vessels	QCA
Funayama 2024 (AsiaIntervention)—Angiographic patterns after DCB angioplasty for de novo lesions	Retrospective observational	Paclitaxel (PCB)	In-segment: 0.24 ± 0.20 mm	46.0%	7 months	De novo CAD	QCA
Scheller 2024—SCB vs. PCB (EuroIntv)	Randomized trial	Sirolimus (SCB) vs. Paclitaxel (PCB)	In-segment: 0.04 ± 0.39 mm	56.3%	6 months	De novo CAD (small-to-medium vessels)	QCA
Ahmad 2022 (JACC Intv)—SCB vs. PCB	Randomized trial	Sirolimus (SCB) vs. Paclitaxel (PCB)	In-segment: 0.01 ± 0.33 mm	60.0%	6 months	De novo CAD (small-to-medium vessels)	QCA

(continued)

Table 17.1 (continued)

Study	Study type	Drug	Late lumen loss (LLL)	% with LLE	Follow-up period	Patient population	Imaging modality for LLE
Onishi 2020 (Cardiovascular Intervention and Therapeutics)	Retrospective observational	Paclitaxel (PCB)	In-segment: 0.03 ± 0.43 mm	56.0%	7 months	De novo CAD (small-to-medium vessels)	QCA
PICCOLETO VI B Cortese 2025 (Asiaintervention 2026, *in press*) [32]	Observational	Sirolimus (SCB) vs. Paclitaxel (PCB)	In-segment: *−0.05 ± 0.56 mm PCB* *0.10 ± 0.59 mm SCB*	58.1% PCB, 40.5% SCB	5 months	De novo CAD (small vessels)	QCA (core lab)

Table 17.2 Summarizes the available data from studies evaluating LLE in de novo CAD other than paclitaxel, focusing on sirolimus-based DCB

Study	Study type	Drug	Late lumen loss (LLL)	% with LLE	Follow-up period	Patient population	Imaging modality for LLE
TRANSFORM I—Ninomiya (JACC Intv)	RCT	Sirolimus (SCB) vs. Paclitaxel (PCB)	In-segment: 0.29 ± 0.48 mm	30.0%	6 months	De novo small-vessel CAD	QCA
Ahmad 2022 (JACC Intv)—SCB vs. PCB	RCT	Sirolimus (SCB) vs. Paclitaxel (PCB)	In-segment: 0.10 ± 0.32 mm	32.4%	6 months	De novo CAD (small-to-medium vessels)	QCA
Scheller 2024—SCB vs. PCB	RCT	Sirolimus (SCB) vs. Paclitaxel (PCB)	In-segment: 0.11 ± 0.37 mm	44.1%	6 months	De novo CAD (small-to-medium vessels)	QCA
Xu et al. 2022 (JACC:CI)	RCT	Biolimus A9 (BCB) vs. POBA (uncoated balloon)	In-segment: 0.16 ± 0.29 mm	29.7%	9 months	De novo small-vessel CAD	QCA

This table includes both randomized controlled trials (RCT) and observational studies

coronary angioplasty (plain old balloon angioplasty, POBA) [35], and 0.6–1.9% after drug-eluting stent implantation [36], with no clear difference between bare-metal stents and DES [37, 38]. Importantly, these figures come largely from the POBA era and non-contemporary DES platforms, so extrapolation to modern devices and current practice should be made with caution.

The mechanisms underscoring LLE have not been fully established. Paclitaxel is a hydrophobic compound, enabling it to penetrate deeply into the arterial wall toward the adventitia, where it prevents smooth-muscle cell proliferation by altering microtubule formation and increasing proapoptotic factor activity [20, 39]. This mechanism promotes vessel expansion (positive remodeling) following DCB-PCI. However, its proapoptotic effects also raise concerns about potential wall thinning and the risk of aneurysm formation over time [33]. Overall, current data to-date suggest that LLE following DCB use is generally associated with favorable outcomes rather than adverse events. More data is need it to define this phenomenon and as well as investigating its appearance with other drugs in the long term.

17.7 Potential Predictors of LLE After DCB Angioplasty for De Novo Coronary Lesions

The known predictors of LLE after DCB-PCI include: (i) pre-procedure thick-cap fibroatheroma and post-procedure deep dissection extending into the tunica media on OCT [18]; (ii) layered plaques and extensive medial dissection with an arc >90° [10]; and (iii) lower angiographic lesion complexity by ACC/AHA classification, LLE being more frequent in less complex lesions; among type C lesions, when LLE is observed it is predominantly in CTO, which tend to show the greatest late lumen increases at follow-up [28]. Controlled plaque dissections are more readily achieved when scoring or cutting balloons are used during vessel preparation prior to DCB use [40–44].

17.8 Conclusion

LLE after DCB treatment appears to be a unique and likely phenomenon. By inhibiting neointimal hyperplasia and promoting positive vessel remodeling, DCB may offer a long-term solution to maintaining vessel patency in the absence of leaving a residual metallic scaffold behind. However, ongoing research is needed to better understand the mechanisms and long-term implications of LLE. As the use of DCB expands, particularly in more complex cases and younger patients, understanding the potential benefits and limitations of LLE is critical. Further research is needed to determine the clinical scenarios where LLE can be optimized, potentially improving the efficacy of DCB in coronary interventions.

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18 The Role of Intravascular Imaging and Physiology Before DCB Angioplasty

Pier Pasquale Leone, Antonio Colombo, Marco Frazzetto, and Bernardo Cortese

18.1 Introduction

Drug-eluting stent (DES) implantation is the most common revascularization strategy for patients undergoing percutaneous coronary intervention (PCI). Although DES demonstrated improved outcomes in comparison to bare metal stents, a permanent metallic scaffold within the vessel carries a life-long risk of device-related complications, primarily in-stent restenosis (ISR) and stent thrombosis. Notwithstanding advances in the field, contemporary devices and techniques still portend a 2%–3% yearly risk of ISR, which increases upon implantation of long and multi-layer stents [1–4]. Since the first preclinical studies in 2004 which demonstrated effective inhibition of restenosis in a porcine coronary model treated with a drug-coated balloon (DCB) [5], these devices underwent substantial refinements for reaching an optimal transfer of the antiproliferative drug into the vessel wall during transient balloon inflation. DCB offer a "metal-free" option that may preserve normal vessel anatomy and function, accelerate arterial healing, potentially favor positive vessel remodeling and avoid implantation of multiple layers of stents in case of failure. Specifically, DCB angioplasty may be preferred for specific clinical settings [6–9], including the following scenarios:

1. ISR (in constrast to the current European guidelines [10]);
2. Small vessel disease;
3. Long lesions, to avoid a "full metal jacket";
4. Complex lesions such as bifurcations and chronic total occlusions, to simplify the procedure.

Intravascular imaging guidance and a physiology-based approach have been well-established as adjuvants to improve clinical outcomes in all-comer patients candidate to coronary stent implantation [10, 11]. We hereby provide contemporary procedural aspects for a DCB-based PCI strategy highlighting the role of intravascular imaging and a physiology in this setting.

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18.2 Procedural Aspects for DCB-Based PCI Strategy

18.2.1 Lesion Preparation

Proper lesion preparation is crucial before DCB angioplasty (Fig. 18.1), as the sole purpose of this approach is the 360° antiproliferative drug delivery to the vessel wall. Routine predilation of crossable de novo lesions with prolonged inflations of non-compliant balloons with 1:1 balloon-to-artery diameter ratio by angiography should aim for full balloon expansion in two orthogonal fluoroscopic views. In case of recoil, cross-over to long inflations (30–60 s) of specialty balloons (e.g., scoring and cutting) should be considered. On the other hand, non-compliant and specialty balloon inflation should be considered at high pressure if insufficient balloon expansion is due to heavy calcification or non-dilatable plaques. In such case, non-compliant, scoring, or cutting balloon undersizing by 0.5 mm based on angiography or 1 mm on intravascular imaging (media-to-media) should be contemplated in order to mitigate potential complications related to balloon diameter yield at high pressure (particularly true for the relatively semicompliant nature of scoring and cutting balloons). In more resistant lesions, gradual inflation of a super-high-pressure non-compliant and/or intravascular lithotripsy balloon should be used. Atherectomy (rotational or orbital) must be considered in recalcitrant or device-uncrossable lesions, particularly when severe calcification is apparent either from angiography or intravascular imaging.

When addressing ISR, besides performing intravascular imaging to asses proper stent expansion, scoring balloons, cutting balloons, very-high-pressure balloons, and laser atherectomy should be liberally utilized.

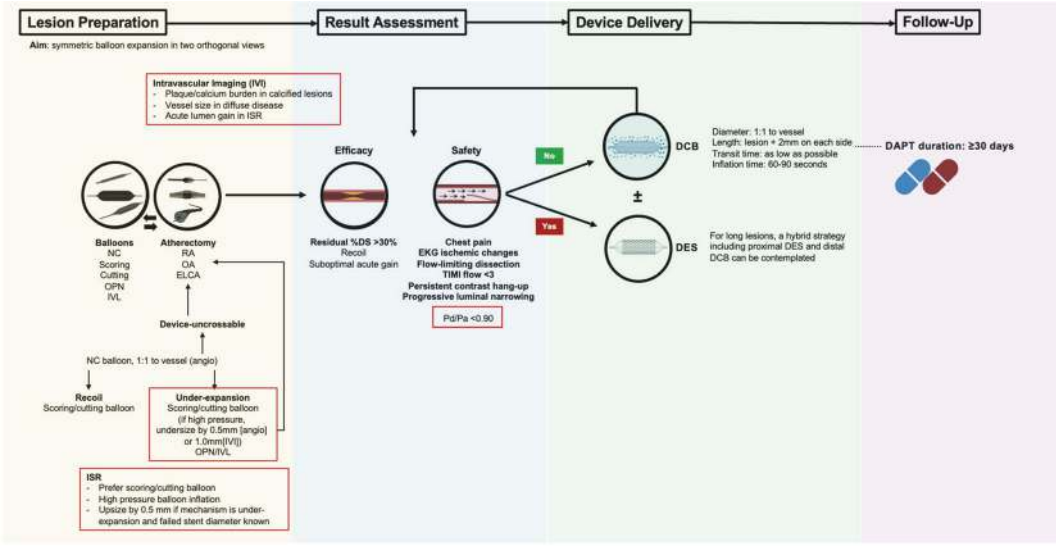


Fig. 18.1 Procedural aspects of DCB-based PCI strategy. A systematic approach to DCB PCI including lesion preparation, result assessment, and DCB angioplasty and/or stenting should be implemented. DAPT: dual antiplatelet therapy, DCB: drug-coated balloon, DES: drug-eluting stent, DS: diameter stenosis, ELCA: excimer laser coronary atherectomy, ISR: in-stent restenosis, IVL: intravascular lithotripsy, NC: non-compliant, OA: orbital atherectomy, Pd/Pa: distal coronary/aortic pressure ratio, RA: rotational atherectomy; TIMI: thrombolysis in myocardial infarction

18.2.2 Result Assessment

Although some of these procedural details might be considered speculative, it is evident that satisfactory lesion preparation before DCB angioplasty, including residual diameter stenosis ≤30%, or <40% in the context of long lesions as stated in the recent DCB ARC document, is associated with a lower risk of recurrent events [6]. More importantly, successful result is supported by the absence of chest pain, ischemic changes on electrocardiography, persistent contrast hang-up, progressive luminal narrowing, flow-limiting dissection, and Thrombolysis In Myocardial Infarction flow <3. In this situation, stent implantation may not be necessary. In the presence of inadequate or unstable result, bailout stenting should be contemplated with the aim to cover the entire dissection if present. Of note, the reported proportion of patients requiring bailout stenting in de novo disease has ranged between 2% and 20%. On the other hand, during treatment of long coronary lesions, an upfront, hybrid strategy entailing proximal segment stenting and DCB angioplasty distally may be an attractive option (Fig. 18.2).

18.2.3 DCB Angioplasty

A DCB with 1:1 balloon-to-artery diameter ratio and a length at least 2 mm longer than the predilated segment at either end should be selected in the majority of cases. Uneventful delivery of the last used (and often bulkiest) balloon can be used as proxy of sufficient support for DCB delivery. DCB delivery to the target lesion is time-sensitive, and, once positioned, the balloon should be inflated to nominal pressures for 60–90 s to

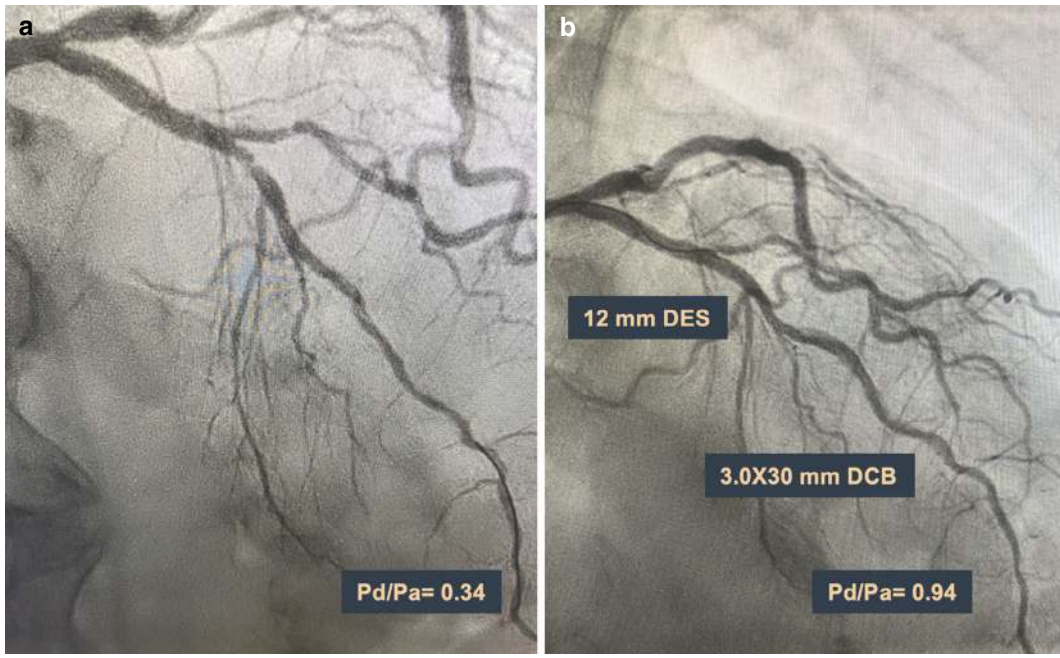


Fig. 18.2 Hybrid approach to avoid "Full Metal Jacket". During treatment of long coronary lesions, an upfront hybrid strategy entailing proximal segment DES implantation and distal DCB angioplasty is an attractive option, particularly for treatment of lesions located in the left anterior descending artery. A final Pd/Pa equal to 0.90 or higher is a favorable index of positive outcome, even in presence of a clear angiographic dissection. Pd/Pa: distal coronary-to-aortic pressure ratio, other abbreviations as in Fig. 18.1

ensure adequate drug delivery. Although no signs of inadequate or unstable result should be expected after low-pressure DCB inflation, result assessment should follow similarly to that occurring after lesion preparation. Additional lesion preparation and DCB angioplasty or stent implantation might then follow as needed.

18.3 Intravascular Imaging

Intracoronary imaging guidance by intravascular ultrasound (IVUS) or optical coherence tomography (OCT) is recommended for performing PCI on anatomically complex lesions, in particular left main stem, true bifurcations, and long lesions. This recommendation derives from solid data suggesting a reduction in adverse clinical events among patients with complex coronary artery lesions when treated via an intravascular-imaging-guided vs. angiography-guided PCI [10–14]. The benefit of intravascular imaging appears to be due to a lower risk of not only repeat revascularization in the stented segment, but also target-vessel-related myocardial infarction or death from cardiac causes. The entirety of such evidence involves PCI conducted with DES implantation, and, thus, most of the observed benefit might derive itself from stent optimization upon appraisal of the information gathered from intravascular imaging.

Recent evidence supports the usefulness of IVUS vs. angiography guidance among patients at high bleeding risk with de novo CAD undergoing DCB angioplasty in achieving a lower late lumen loss, larger minimal lumen diameter and lower diameter stenosis [15]. Nonetheless, such study did not include patients with long lesions, and the authors did not point out the criteria utilized to guide the procedure with IVUS by defining the "acceptable optimal result" in terms of lumen size, residual stenosis and extent of dissection at IVUS. In addition, the approach utilized to improve results when initial IVUS evaluation showed an insufficient residual lumen, as well as whether and how dissection evaluation at IVUS changed the management of any lesion, were not clarified [16, 17]. Of note, extensive medial dissection after paclitaxel-coated balloon angioplasty was associated with higher late lumen enlargement occurrence in 108 de novo coronary lesions in a recent observational retrospective study adopting serial OCT measurements [18]. As a matter of fact, the question of whether angiography is enough to evaluate safety and efficacy of DCB angioplasty still remains. Arguably, the absence of any stent to optimize simplifies the procedure, and it is conceivable that angiography guidance might be suitable for treatment of long non-calcific lesions, as long as reference vessel diameter can be reasonably estimated to ensure proper DCB sizing and drug delivery to the vessel wall. On the other hand, intravascular imaging remains conceptually key to assess the following aspects in specific scenarios:

1. Plaque and calcium burden in complex lesions;
2. Lumen gain in ISR;
3. Vessel size in diffuse disease.

In general, IVUS is routinely preferred, in our experience, to avoid the rheolytic insult related to the high flow and volume injections needed for OCT. Nevertheless, OCT was effectively utilized to evaluate the predilatation result prior to DCB [19].

18.3.1 Calcified Lesions

Severe coronary artery calcification (CAC) can be encountered in up to 30% of patients with coronary artery disease, and its percutaneous

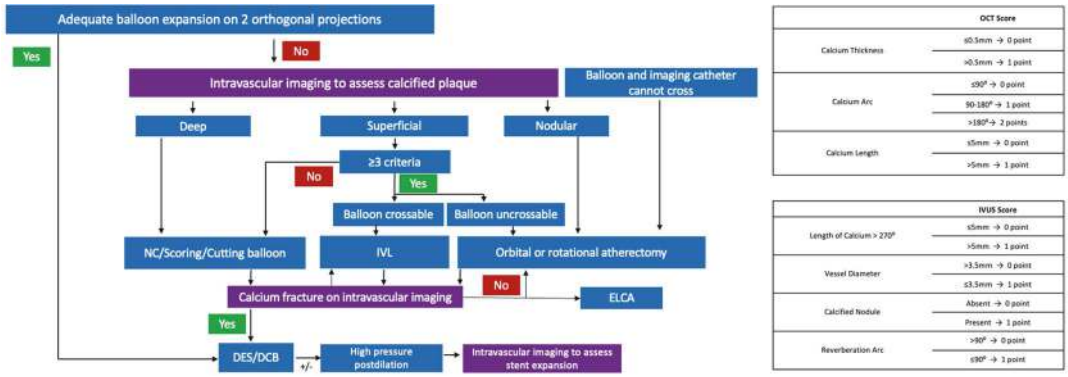


Fig. 18.3 Real-World Algorithm for PCI in Calcified Lesions. On the left, an indicative algorithm for real-life management of calcified lesions. In purple, the instances where intravascular imaging can be useful to guide PCI in calcified lesions. On the right, a list of criteria important to assess at intravascular imaging to guide the procedure. OCT: optical coherence tomography, other abbreviations as in Fig. 18.1

management remains a challenge. Lesions with severe CAC often present larger plaque burden and are more complex, so that patients are less likely to receive complete revascularization and have a higher risk to develop adverse events, including death [20]. DCB angioplasty might simplify the procedure in many instances, as long as appropriate lesion preparation is achieved. In this context, intravascular imaging is key to guide choice of the proper calcium debulking strategy (Fig. 18.3). Of note, undersizing by 0.5 mm on angiography or 1 mm on intravascular imaging (media-to-media) should be aimed when utilizing high-pressure balloon inflation with scoring or cutting balloon for non-dilatable segments (Fig. 18.4). This combines the action of the scoring element and microblades and the high inflation pressure exerted on a delimited surface for achieving plaque modification. In addition, intravascular imaging can be useful to assess calcium fracture, as a proxy of satisfactory lesion preparation. Finally, according to the result assessment, the decision to proceed with DCB angioplasty or DES implantation can follow.

18.3.2 Diffuse Disease

At coronary angiography, diffuse disease is defined as a long coronary segment (≥20 mm) with angiographic irregularities in the absence of a clear focal stenosis. Diffuse disease is considered a marker of poor prognosis with limited treatment options, and is one of the underlying mechanisms of persistent angina after PCI [21]. Although alternatives should be considered, such as optimal medical therapy or coronary artery bypass graft surgery in presence of extensive disease with reasonable distal targets, DCB angioplasty permits to avoid overstenting when PCI remains the best option. Intravascular imaging should be used to optimize outcomes by ensuring adequate vessel sizing (after use of vasodilators), with the aim, on one hand, to avoid flow-limiting dissections due to balloons oversizing, and, on the other hand, to ensure contact between balloons and vessel wall and effective drug delivery to the target lesion (Fig. 18.5).

The use of physiology (see Sect. 18.4.2) monitoring distal coronary-to-aortic pressure ratio

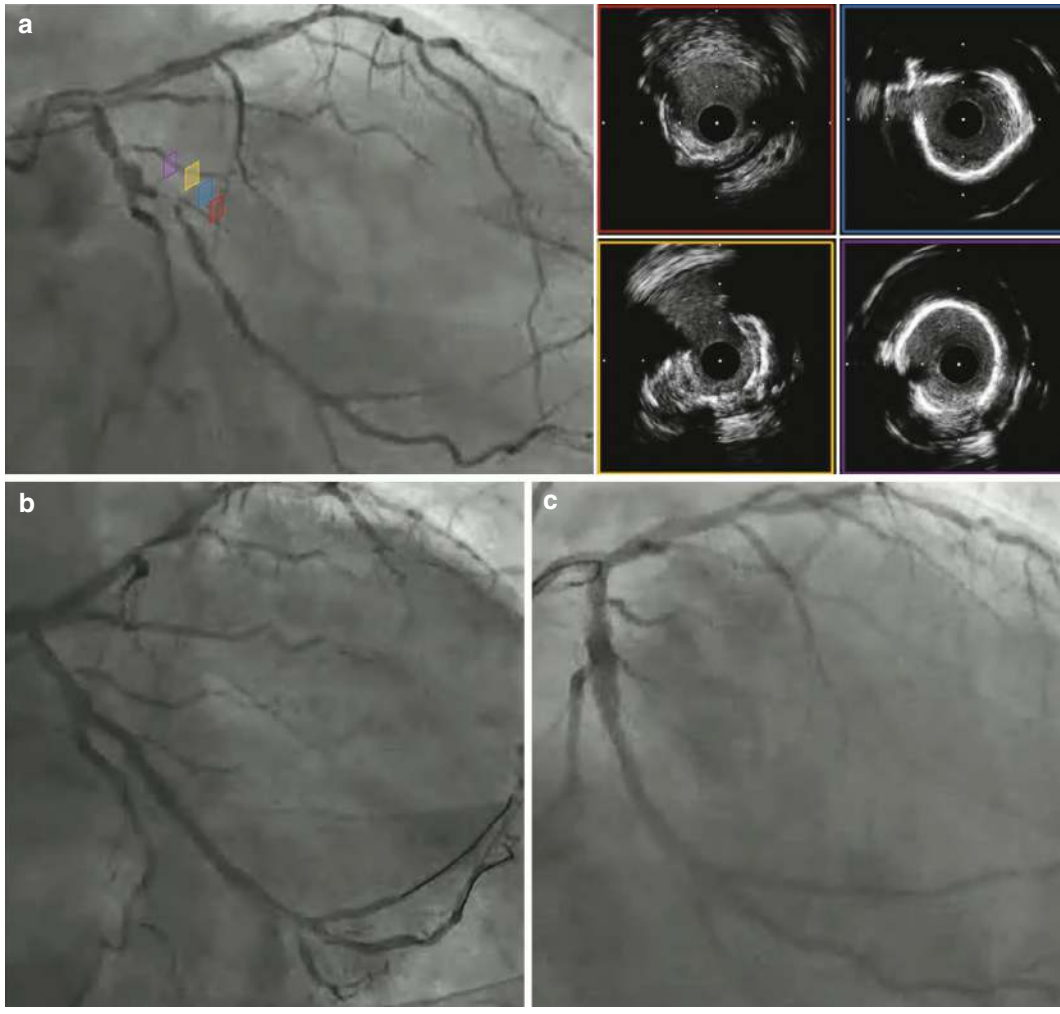


Fig. 18.4 Intravascular imaging for calcified lesions. Predilation of the subtotal occlusion in the proximal Left Circumflex Artery with a 2.0 mm balloon was required for advancement of IVUS through the lesion. IVUS revealed a calcium arc larger than 180°, extending deep into the vessel wall and >5 mm along the vessel (**a**). Optimal lesion preparation was achieved via high-pressure inflation of a 3.0 mm cutting balloon was followed by 3.5 mm IVL balloon inflation, in absence of flow-limiting dissection (**b**). Implantation of a 3.5 × 23 mm DES and DCB angioplasty with 3.0 × 30 mm sirolimus-coated balloon followed, and the final result is shown in (**c**). IVUS: intravascular ultrasound, other abbreviations as in Fig. 18.1

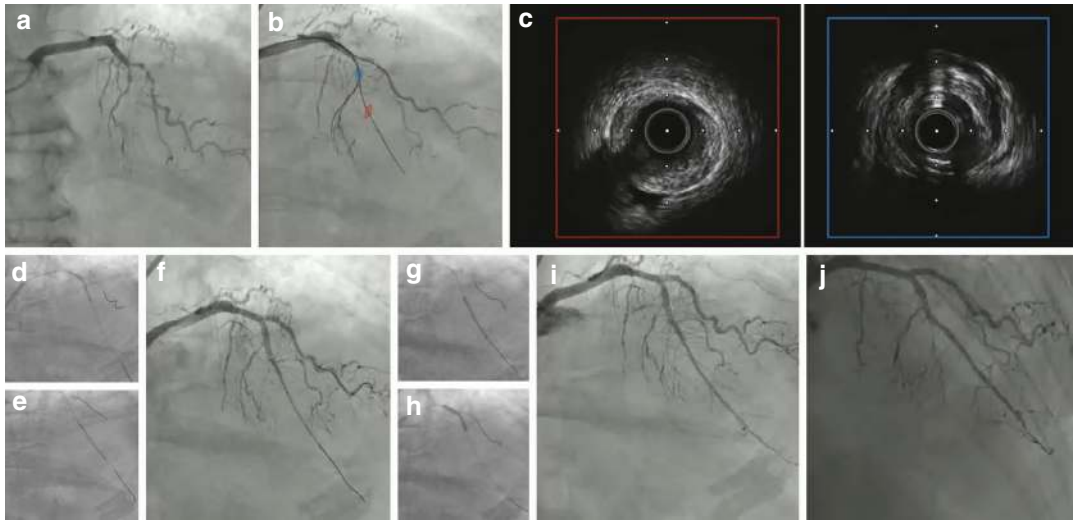


Fig. 18.5 Intravascular imaging for diffuse disease. A LAD chronic total occlusion in its mid segment and long diffuse disease of a large first diagonal branch were evident at angiography (**a**). Successful crossing of the occlusion was followed by IVUS (**b**), which showed diffuse severe concentric atheromasia in absence of heavy calcification (**c**). Successful lesion preparation with 2.5 mm NC balloon in mid-distal LAD and diagonal branch and 3.0 mm NC balloon in proximal LAD (**d**, **e**) was evident at angiography (**f**). DCB angioplasty with paclitaxel-coated balloons in LAD (3.0 × 30 mm and 2.5 × 30 mm) and diagonal branch (2.5 × 30 mm) followed (**g**, **h**) and an optimal angiographic result with a type B non-flow-limiting dissection in the distal LAD was evident (**i**). One-year follow-up angiography revealed a sustained angiographic result (**j**). LAD: left anterior descending artery, other abbreviations as in Fig. 18.3

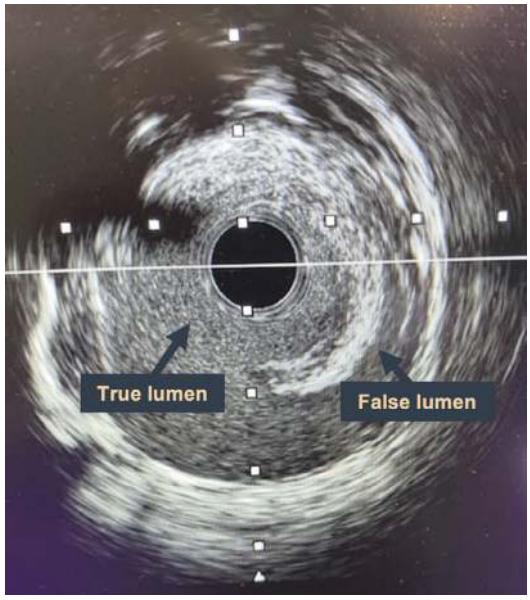


Fig. 18.6 Intravascular imaging usefulness for dissections stratification. In order to implement a DCB strategy the operator needs to understand which dissections can be tolerated. Intravascular imaging is useful, though not mandatory, for this decision-making. As depicted in the figure, a large true lumen, with a relativaly small false lumen, represents a key element to define a dissection as "benign"

(Pd/Pa) and final FFR is frequently utilized during treatment of long lesions and diffuse disease to evaluate progress made during lesion preparation and assess the hemodynamic impact of a dissection. The presence of a final Pd/Pa equal to 0.90 or higher has often been a favorable index of positive outcome, even when a clear angiographic dissection is present. This fact is confirmed by the presence of a large residual lumen when evaluated with intravascular imaging (Fig. 18.6). Despite the value of intravascular imaging and/or residual pressure gradient to establish the appropriateness to leave a dissection without stent implantation, in clinical practice the combination of the following three elements (all 3 need to be present to define an optimal result) is the most widely used strategy for decision-making: (1) fast dye clearing from the dissection plane, (2) residual lumen 70% or more in two orthogonal angiographic projection and (3) Thrombolysis In Myocardial Infarction (TIMI) 3 flow (Fig. 18.7).



Fig. 18.7 The value of angiography to establish the appropriateness to leave a Dissection. Despite the value of intravascular imaging and/or residual pressure gradient, in clinical practice the concomitant presence of the following three elements has been, in our experience, the most widely used strategy for decision-making: (i) fast dye clearing from the dissection plane (i.e., no contrast hang-up), (ii) residual lumen 70% or more in two orthogonal angiographic projection, and (iii) TIMI 3 flow. These characteristics were all present when evaluating the linear dissection depicted in the figure (blue arrow), and no stent implantation followed

18.3.3 In-Stent Restenosis

Optimal lesion preparation has been shown to reduce event rates after DCB interventions of ISR, with the use of scoring balloons tending to improve results. Even more so, intravascular imaging allows to understand the underlying mechanism of ISR, which has therapeutical implications. Indeed, lesions suggesting neointimal hyperplasia or neoatherosclerosis might be better off after angioplasty with special balloons, such as scoring or cutting, while ISR lesions due to under-expanded stents might benefit more from high-pressure inflation of non-compliant or super high-pressure balloons. In addition, intravascular imaging is particularly useful to assess acute lumen gain after lesion preparation and before DCB angioplasty (Fig. 18.8). Optimal target minimal stent area values according to size of the balloon adopted can be extrapolated from the Angiography Vs. IVUS Optimization study [22]. This approach is in apparent contradiction of what recently suggested by the European

Fig. 18.8 Intravascular imaging for ISR. An ISR lesion was evident within a previously implanted DES in the mid LAD (**a**). IVUS revealed good stent expansion, and the images were compatible with calcific neoatherosclerosis within the stent struts (**b**). Lesion preparation with a 3.0 × 15 mm NC balloon high-pressure inflation (**c**, **d**) and 3.5 × 10 mm cutting balloon (**e**) yielded a good acute lumen gain and an optimal result at both angiography (**f**) and IVUS (**g**). Angioplasty with a 3.5 × 30 mm sirolimus-coated balloon followed (**h**), and a final optimal angiographic result was confirmed (**i**)

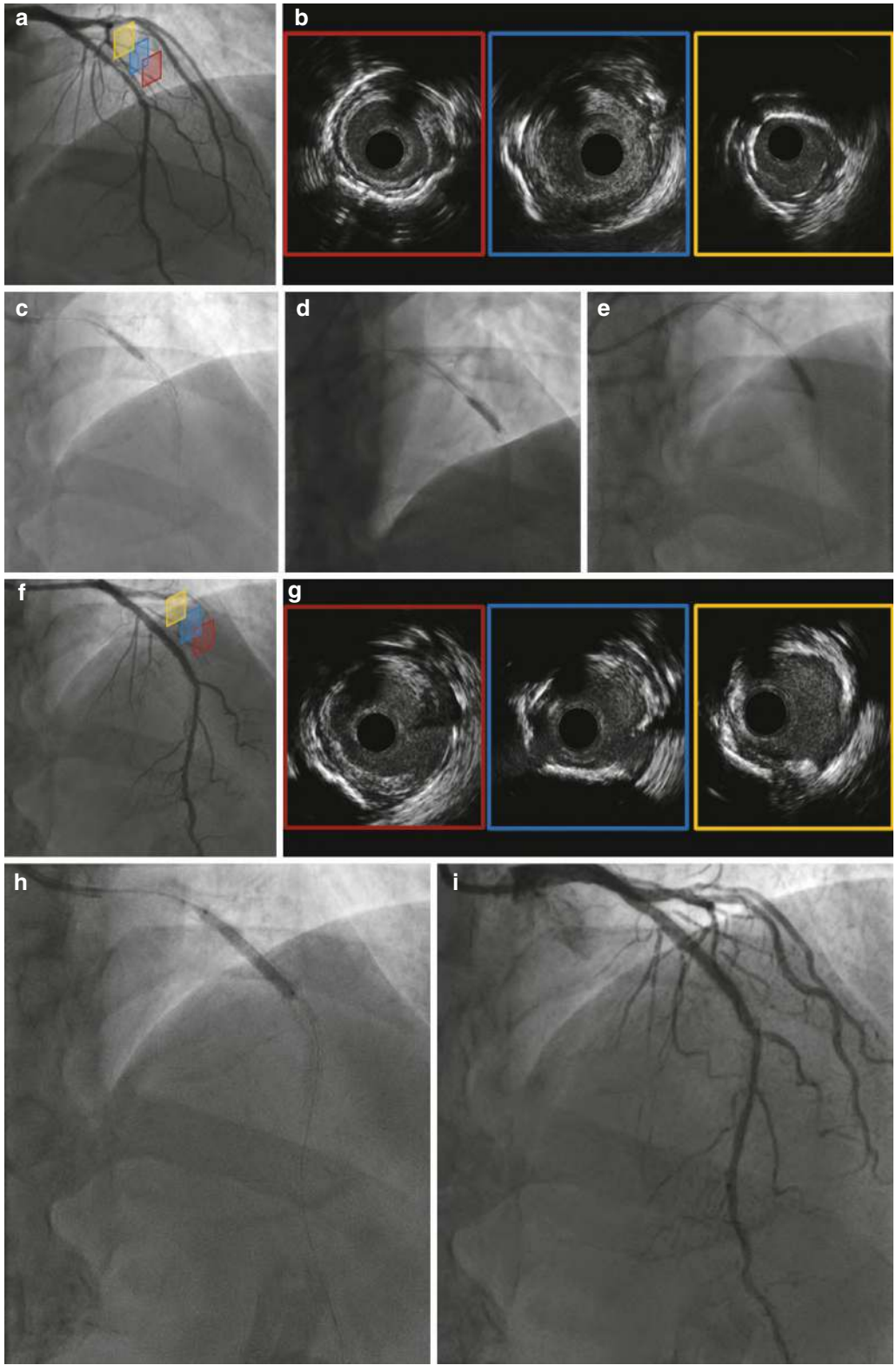


Fig. 18.8 (continued)

guidelines for DES-ISR giving a Class I level of evidence A for DES over DCB [10]. We believe that this new recommendation, supported by a recent meta-analysis of several studies evaluating DES versus DCB [23], included some studies where the lesion preparation prior to DCB was not optimal. For this reason we agree that stenting should be considered for DES-ISR when optimal lesion preparation cannot be obtained due to recoil or plaque prolapse.

18.4 Physiology

Coronary hemodynamic measurements aim to identify the impact of coronary artery disease on coronary flow, assuming that impaired myocardial perfusion and myocardial ischemia predict adverse clinical outcomes. Fractional flow reserve (FFR) is defined as the ratio between distal coronary pressure (Pd) and aortic pressure (Pa) during steady-state hyperemia, and it is recommended to guide revascularization decision-making in intermediate-severity coronary stenosis. Non-hyperemic pressure ratios are alternatives measuring Pd/Pa in resting conditions, and, among them, the instantaneous wave-free ratio (iFR) calculates such ratio during a period of diastole known as the "wave-free period," and was demonstrated to be non-inferior to FFR in large randomized clinical trials. Recently, angiography-derived indexes including quantitative flow ratio (QFR) have been developed to compute FFR by combining three-dimensional vessel reconstruction and computational fluid dynamics, obviating the need for the use of pressure wire technology and hyperemia induction [11].

18.4.1 Indication to Pursue PCI

Selective assessment of functional severity of intermediate diameter stenoses is recommended to guide the decision to revascularize using FFR/iFR (significant ≤0.80 or ≤0.89, respectively) or QFR (significant ≤0.80). This indication persists regardless of the planned PCI strategy, that is, DES implantation or DCB angioplasty [11].

18.4.2 Result Assessment After Lesion Preparation

FFR values after PCI are generally considered to reflect residual disease. Its clinical relevance after DES implantation has been explored, and a low post-PCI FFR was found to be common and demonstrated a significant and inverse association with adverse clinical events. In the setting of residual dissections and angiographically limited acute lumen gain after lesion preparation, the use of FFR has been advocated to better define the functional result before DCB angioplasty, although evidence on the optimal cut-off is not univocal [6]. Despite this, an FFR value ≥0.75 emerged as a reliable cut-off for identifying lesions suitable for DCB treatment, ensuring comparable clinical outcomes with DES, with adequate anatomical and physiological patency during follow-up re-assessment. In addition, it was reported that in the left anterior descending artery the majority of lesions with angiographically severe dissection had an FFR ≥0.75, suggesting that angiographic judgment of dissection severity may not have a corresponding hemodynamic impact [25]. Neverthelsss, more powered and prospective studies are awaited for validating such approach.

When planning a DCB-based PCI strategy, one of the most common and important aspects is the assessment of the influence of uncomplicated dissection after lesion preparation on immediate and long-term outcomes. Indeed, while a flow-limiting dissection is a straightforward indication to DES implantation, there is no consensus on management of an uncomplicated dissection in the real-world, although a recent consensus states that any National Heart, Lung, and Blood Institute type C or greater dissection should be treated with stent implantation [26]. Nonetheless, the discussion remains open, considering also recent findings that extensive medial dissection after DCB angioplasty was associated with higher late lumen enlargement occurrence in de novo coronar y lesions [18, 27–33]. Inspired by evidence from almost fourty years ago suggesting that an uncomplicated intimal dissection after a successful coronary angioplasty has no adverse

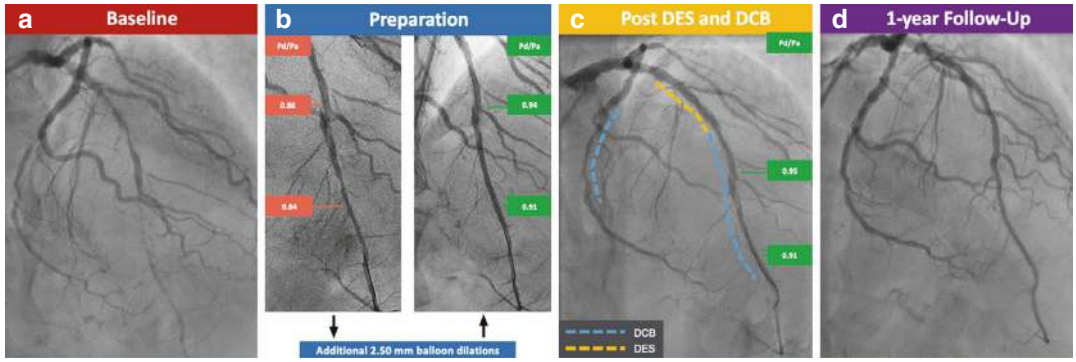


Fig. 18.9 Pd/Pa for assessment of result stability after lesion preparation. Long calcific disease of left anterior descending artery (**a**) treated via hybrid strategy including proximal 3.5 × 23 mm DES implantation and mid-distal distal coronary-to-aortic pressure ratio (Pd/Pa)–guided 2.5 × 40 mm Sirolimus-coated balloon angioplasty (**b**). The optimal final result (**c**) was persistent at 1-year follow-up angiography (**d**). Dashed blue and orange lines indicate location of DCB angioplasty and DES implantation, respectively

influence on angiographic restenosis [24], we recently found a Pd/Pa ≥0.90 to predict favorable evolution of coronary dissections (Fig. 18.9). Finally, angiography-derived physiological index like the quantitative flow ratio (QFR) and Murray's law-based QFR (μQFR) measured after DCB angioplasty may play an important role in the decision-making. Although at an embryonic stage and assessed in small retrospective studies, this methodologies appear to well predict future events (even though a specific post DCB angiosplaty should be established) and the need for further optimization after DCB angioplasty [34–36].

18.5 Conclusion

DCB angioplasty has emerged as an alternative approach for certain patients undergoing PCI. Intravascular imaging and physiology guidance [37] are current standards of care for patients undergoing (complex) stent implantation, and, similarly, both have the potential to be relevant adjuvants to ensure procedural safety and efficacy among patients undergoing DCB angioplasty. Solid data is currently missing in this setting, and dedicated prospective studies to evaluate their respective roles are eagerly awaited.

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19 Final Assessment After DCB Angioplasty: Is Angiography Sufficient?

Denis Leonardi, Alessandro Sarai, Bernardo Cortese, and Simone Fezzi

19.1 Introduction

The introduction of coronary stents during percutaneous coronary intervention (PCI) was intended to address the limitations of plain old balloon angioplasty by preventing acute vessel recoil, sealing flow-limiting dissections, and reducing restenosis caused by acute barotrauma [1, 2]. Drug-eluting stents (DES) have since demonstrated both safety and efficacy in lowering the incidence of device- and vessel-oriented adverse events, leading to their strong endorsement in current clinical guidelines [3, 4]. Nonetheless, the implantation of permanent metallic devices carries inherent limitations. The need for prolonged dual-antiplatelet therapy (DAPT) may increase bleeding risk, particularly in elderly individuals and those deemed at high bleeding risk (HBR) [5, 6]. In addition, contemporary DES are still associated with a persistent incidence of late stent-related complications, such as in-stent restenosis, stent thrombosis, and neoatherosclerosis, occurring at approximately 2%–3% per stent per year, even beyond the first year after implantation [7–9].

The use of drug-coated balloons (DCBs) for treating de novo coronary artery disease (CAD) aims to prevent restenosis by delivering an antiproliferative drug into the arterial wall without permanently caging the vessel [10].

This "leave-nothing-behind" strategy is particularly attractive in patients at increased risk of implant-related adverse events. Such situations often include complex coronary anatomies, such as small vessels, bifurcations, chronic total occlusions, calcified or diffusely diseased segments, and clinical settings characterized by higher procedural or bleeding risk, including diabetes mellitus, HBR, and chronic kidney disease. Notably, these conditions frequently coexist within the same patient, further strengthening the rationale for a stentless approach. Recent evidence demonstrates that DCB provide clinical and angiographic outcomes comparable to DES in small vessels, with sustained efficacy for up to 3 years [11]. The relatively low rate of restenosis observed after PCI of native coronary artery stenoses using DCB, despite their lower acute luminal gain compared with DES, is largely attributed to positive vessel remodeling, which is reported in approximately two-thirds of lesions treated with paclitaxel-coated DCB, and one-third with sirolimus-coated DCB [12–15].

Proper lesion preparation is a pivotal procedural step to ensure optimal DCB performance.

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To date, its adequacy has primarily been evaluated through angiographic assessment in clinical trials [5, 11]. However, these recommendations are largely based on expert opinion rather than robust, evidence-based data, and standardized criteria for defining adequate preparation remain under investigation.

In this chapter we aim to provide a comprehensive overview of the evaluation of procedural result after DCB-only PCI, focusing on angiographic assessment, physiological evaluation and intracoronary imaging techniques.

19.2 Angiography-Based Assessment: The Standard Reference

In de novo lesions, lesion preparation using semi-compliant or non-compliant balloons with a balloon-to-artery ratio of 1:1 based on the distal reference vessel diameter (RVD) is recommended, and the result should be carefully reassessed before DCB delivery [11]. Indeed, angiographically inadequate lesion preparation prior to DCB inflation has been reported as an independent predictor of target lesion revascularization (TLR) in the setting of in-stent restenosis [16]. Cutting/scoring balloons are recommended when adequate lesion preparation cannot be achieved with standard techniques. Prolonged inflations, typically exceeding 30 s, are advised for lesion preparation, while even longer inflations (≥60 s) are preferred during final DCB deployment [17, 18]. A recent study demonstrated that lesion preparation using scoring balloons, compared with non-scoring balloons, significantly reduced the risk of severe dissection and increased the likelihood of optimal angiographic results, defined as Thrombolysis In Myocardial Infarction (TIMI) 3 flow, residual diameter stenosis ≤30%, and dissection less than Type C after the procedure [19]. Consistently, in the REC-CAGEFREE I trial, pre-dilation with scoring or cutting balloons was commonly adopted and outcomes within the cutting balloon subgroup were comparable between DCB and DES across different lumen dimensions (4.8% vs. 3.6%; HR 1.24, 95% CI 0.61–2.55; $p = 0.557$) [20].

Although lesion preparation is universally recognized as a key determinant of procedural success in DCB angioplasty, current recommendations remain largely based on expert consensus rather than robust, prospective evidence. According to international DCB consensus recommendations [5], an optimal balloon angioplasty requires: (1) full balloon expansion with appropriate vessel sizing; (2) ≤30% residual stenosis by visual estimation; (3) TIMI flow grade 3; (4) absence of a flow-limiting dissection. However, visual estimation of post-DCB angiographic results is subject to considerable inter-operator variability (≥10%) [21]. Therefore, at least in clinical trials, quantitative coronary analysis is recommended to ensure objective and reproducible assessment [22]. The DCB Academic Research Consortium (DCB-ARC) recently defined DCB-PCI success with a residual diameter stenosis <40% using offline QCA, with possible stratification in optimal result if DS < 30% and suboptimal if DS between 30% and 40% [23, 24].

Of note, coronary angiography should exclude delayed contrast clearance within the vessel lumen, arterial wall, or any dissection plane. Two final orthogonal angiographic projections, preferably matching the pre-procedural views, are required to confirm the absence of significant dissections. Post-PCI dissections are conventionally classified according to the National Heart, Lung, and Blood Institute (NHLBI) classification derived from pre-stent era data [25].

Angiographically-defined Type A and B dissections are relatively common (10%–15% of cases) and have long been considered safe to leave untreated after balloon angioplasty. These minor dissections are generally well tolerated, do not require additional stenting or major intervention, and can be safely managed with medical therapy and close clinical follow-up, typically demonstrating complete angiographic healing without significant neointimal hyperplasia [26, 27]. The clinical significance of Type C dissections remains a matter of ongoing debate. Recent data suggest favorable mid-term outcomes, with

spontaneous sealing of dissections and minimal neointimal proliferation [27]. Nevertheless, in general, any Type C or higher dissection should prompt consideration for stent implantation [5].

Recent expert consensus documents have evolved beyond a purely anatomical classification, proposing an angiography-based assessment that integrates functional parameters, including flow limitation (TIMI frame counting), EKG changes, and patient symptoms (e.g., chest pain), to guide the decision on whether to crossover to stent [10].

19.3 Coronary Physiology

19.3.1 Pressure-Wire-Based Physiology

Pressure-wire- and angiography-based functional assessments can support decision-making in coronary revascularization. To date, however, no prospective, dedicated clinical studies have specifically evaluated the role of invasive, pressure-wire-based coronary physiology in guiding DCB treatment. The REDUCE-STENT (dRug-coatED balloon angioplasty gUided by post-perCutanEouS coronary inTErvention pressure gradieNT) retrospective registry evaluated Pd/Pa ratios after lesion preparation and following DCB [28], to guide the decision between DCB-only PCI and eventual added stenting in complex lesions located in large size vessels. A DCB-only strategy was deemed safe and feasible when post-procedural Pd/Pa was >0.90.

Hyperemic fractional flow reserve (FFR) assessment provides a more reliable assessment of coronary ischemia and can be used to define the immediate functional result [29, 30]. An FFR value above the ischemic threshold may be considered sufficient to defer stent implantation. In a meta-analysis of DES-PCI, optimal post-PCI FFR cutoffs were 0.86 for predicting target vessel failure (TVF), while 0.80 for the composite of cardiac death and target vessel myocardial infarction at 2 years [31]. Earlier evidence suggested that FFR > 0.90 combined with coronary flow reserve > 2.5 after balloon angioplasty was associated with immediate functional improvement and low restenosis rates at short-term follow-up [32, 33]. Subsequent studies, however, have explored slightly lower functional thresholds. For instance, DCB-only PCI guided by an FFR ≥ 0.85 after plain old balloon angioplasty (POBA) was shown to be safe and effective for de novo lesions, with lower late lumen loss and similar 9-month FFR and 1-year adverse events rates compared with stenting [34]. Likewise, DCB treatment guided by FFR > 0.80 after POBA was safe in stable CAD, even with short DAPT (4 weeks), and demonstrated a trend toward positive vessel remodeling (net luminal gain) without diameter loss at 6 months [26]. Favorable results were also reported in lesions with FFR ≥0.75, showing lower late lumen loss in the DCB-only group compared with DES, with no significant differences in clinical outcomes at 1 year [35]. In a prospective observational study, higher FFR and/or iFR values measured 15 min after DCB angioplasty predicted late lumen enlargement (LLE) at 9-month follow-up. Moreover, a smaller difference between immediate and 15-min post-DCB physiological values was observed in patients who developed LLE, suggesting that early physiological stabilization may predict favorable vascular remodeling [36]. Clinical studies investigating the role of coronary physiology in DCB-only PCI are listed in Table 19.1, while a case of DCB-PCI guided by physiological assessment using FFR and iFR is reported in Fig. 19.1.

19.3.2 Angiography-Based Physiology

Novel angiography-based physiological solutions offer several potential advantages in the context of DCB-PCI [7]. Quantitative parameters such as the TIMI frame count enable functional evaluation without the need for pressure wires or hyperemic agents. These indices inherently incorporate flow-related information, which is crucial especially in case of dissections. Moreover, they can be easily obtained during routine angiographic acquisition, and are co-registered with angiographic landmarks,

Table 19.1 Overview of coronary physiology-guided DCB–PCI studies

Coronary physiology				
Study/author	Design/setting	Technique/ physiologic index	Population/lesions	Key findings/main outcomes
Leone et al., *JACC Interventions* (2023) (REDUCE-STENT)	Retrospective registry, proof-of-concept De novo lesions	Pressure wire (Pd/Pa) post-lesion preparation	86 pts., 109 complex lesions (medium–large vessels)	Post-DCB Pd/Pa > 0.90 → DCB-only strategy safe and feasible
Shin et al., *CCI* (2016)	Prospective single-center registry De novo lesions	FFR after lesion preparation	66 pts. (67 de novo lesions: 45 DCB, 22 DES) (medium–large vessels)	FFR ≥ 0.85 post-POBA → lower LLL → comparable 1-yr MACE vs. DES
Poerner et al., *Clinical Research in Cardiology* (2017)	Prospective, single-center, single-arm (OCTOPUS-2) De novo lesions	FFR after POBA	Stable CAD, 46 pts. (43 pts. and 51 lesions DCB; 3 pts. and 3 lesions DES) (small-medium vessels)	FFR > 0.80 safe with 4—wk. DAPT; positive remodeling, no LLL at 6 months (LLL: −0.13 ± 0.44 mm, n.s.; OCT—NLG: 1.10 ± 0.53 mm, $p < 0.001$)
Her et al., *Int J Cardiovasc Imaging* (2018)	Prospective observational, single-center registry De novo lesions	FFR after POBA	Elective PCI for de novo lesion (2.5–3.5 mm, ≤ 24 mm length), 200 POBA-FFR FFR ≥ 0.75 78 DCB and 73 DES. FFR < 0.75 49 DES (medium–large vessels)	FFR ≥ 0.75 → lower LLL with DCB-only; no outcome differences between the 3 subsets at 1 yr
Yamamoto et al., *Int J Cardiol* (2022)	Prospective observational, single-center De novo lesions	FFR/iFR post—DCB	50 lesions (OCT-guided DCB, 9-mo FU), 2 FU groups: 29 LLE, 18 non-LLE (3 bail-out stenting) (medium vessels)	Late lumen enlargement predicted by: Higher FFR/iFR 15 min after DCB Lower dif-FFR/dif-iFR
RESTORE-SVD (Li et al., *Int J Cardiol* 2021)	Post-hoc of prospective RCT De novo lesions	QFR post—DCB	230 pts. (116 DCB vs. 114 DES, small vessels)	9-mo QFR & QFR loss correlated with LLL → supports QFR for functional evaluation
PICCOLETO VI Fezzi et al. AsiaIntervention (2026)	Multicenter retrospective De novo complex lesions	2D-μFR post DCB	227 pts., DCB –PCI	μFR ≤0.86 post-DCB predicted ischemia → AUC 0.758; (95% CI 0.697–0.812; $p < 0.001$) →%DS not predictive
Garin et al., *CCI* (2025) (CARDIO-FR registry)	Prospective registry, single-center De novo lesions	3D-μQFR post—DCB	81 pts., 87 DCB-treated de novo lesions (all vessels)	Post-procedural μQFR lower in VOCE lesions (0.76 vs. 0.90, $p < 0.001$); cutoff 0.83 (AUC 0.74; HR 6.01, $p < 0.001$).
Wang C. et al., *CCI* (2025)	Retrospective analysis, single-center In-stent restenosis	3D-QFR	108 pts. (38 restenosis, 70 non-restenosis)	Lower QFR post-DCB in restenosis, independent predictor (AUC 0.727 [95% CI: 0.518–0.936], $p < 0.05$)

(continued)

Table 19.1 (continued)

Coronary physiology				
Study/author	Design/setting	Technique/ physiologic index	Population/lesions	Key findings/main outcomes
Lin et al, BMC *Cardiovascular Disorders* (2024)	Post-hoc of multicenter RCT De novo lesions	3D-QFR	DCB—PCI pts. (vessel 2.0–2.75 mm): 175 with QFR ≥ 0.86 and 111 with QFR < 0.86. Small vessels	QFR < 0.86 → higher MACE (27% vs. 5.7%, HR 3.63, $p < 0.001$) ΔQFR <0.57 → MACE 20.2% vs. 4.4% (HR 4.70, $p < 0.001$)
Liu L. et al., *Cardiol J* (2023)	Post-hoc of multicenter RCT In-stent restenosis	μQFR (ISR DCB cohort)	169 ISR pts. with 169 lesions	μQFR ≤0.89 → higher VOCE (AUC 0.74 vs. 0.61 for %DS; HR 5.94, $p < 0.001$).

CAD coronary artery disease, *DAPT* dual antiplatelet therapy, *DES* drug-eluting stent, *DCB* drug-coated balloon, *FFR* fractional flow reserve, *FU* follow-up, *IVUS* intravascular ultrasound, *iFR* instantaneous wave-free ratio, *LLE* late lumen enlargement, *LLL* late lumen loss, *MACE* major adverse cardiac events, *μFR/μQFR* angiography-derived or Murray law-based quantitative flow ratio, *n.s.* not significant, *%DS* percent diameter stenosis, *PCI* percutaneous coronary intervention, *Pd/Pa* pressure distal to pressure proximal (pressure wire ratio), *POBA* plain old balloon angioplasty, *OCT* optical coherence tomography, *ISR* in-stent restenosis, *VOCE* vessel-oriented composite endpoint, *HR* hazard ratio, *AUC* area under the curve

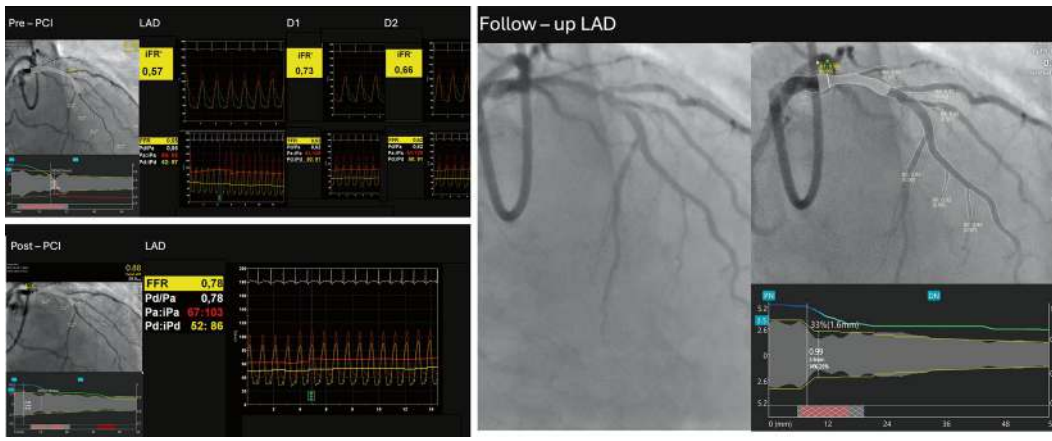


Fig. 19.1 Physiology-guided DCB–PCI for a severely calcified trifurcation. *Left panel*: Pre-procedural functional assessment demonstrated hemodynamically significant ischemia. Invasive pressure-wire assessment confirmed physiological impairment with an LAD iFR of 0.57 and FFR of 0.55, and involvement of the side branches (D1: iFR 0.73, FFR 0.62; D2: iFR 0.66, FFR 0.62). Lesion preparation was performed with sequential balloon pre-dilatation using a 2.0 mm semi-compliant balloon, followed by intravascular lithotripsy (IVL) with a 2.5 mm balloon to optimize lesion compliance. Further optimization was achieved using a 3.0 mm non-compliant balloon in the mid LAD and a 2.5 mm semi-compliant balloon in D1. Subsequently, sequential DCB inflations (3.0 × 30 mm in the mid LAD and 2.5 × 20 mm in D1) were performed. Post-procedural physiological reassessment confirmed substantial improvement in epicardial flow, with μFR increasing to 0.88 and invasive FFR improving to 0.78, indicating a satisfactory functional result without the need for stent implantation. *Right panel*: At angiographic follow-up, the treated segments demonstrated persistent luminal gain and excellent vessel patency. Non-invasive μFR assessment documented complete functional recovery, with a value of 0.97 in the LAD, confirming sustained physiological benefit after stentless DCB-PCI in this complex calcified trifurcation. D1, D2 = first and second diagonal branches; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LLE = late lumen enlargement; LLL = late lumen loss; MACE = major adverse cardiac events; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; Pd/Pa = pressure distal to pressure proximal (pressure wire ratio); μFR = angiography-derived or Murray law-based quantitative flow ratio

facilitating lesion-level assessment and procedural guidance. However, their application may be limited by interpretation challenges in the presence of extensive vessel dissections, which can alter contours definition, contrast transit and confound flow-based measurements.

In a cohort of patients treated with DCB-PCI for ISR (n = 169), post-procedural Murray's law-based quantitative flow ratio (μFR) demonstrated strong predictive accuracy for vessel-oriented composite outcomes (VOCE; area under the curve (AUC) 0.74; 95% CI 0.67–0.80; $p < 0.001$), outperforming post-procedural in-stent percent diameter stenosis (AUC 0.61; 95% CI: 0.53–0.68; $p = 0.18$). A μFR ≤ 0.89 value strongly predicted VOCE (HR 5.94; 95% CI: 2.33–15.09; $p < 0.001$) [22]. Similarly, a post-hoc analysis of the RESTORE Small Vessel Disease study found that QFR loss at 9 months correlated positively with late lumen loss, particularly in DCB-treated patients, further supporting the role of physiological assessment in small-vessel DCB-PCI [23].

In the PICCOLETO VI study (227 patients), post-PCI μFR showed a significant association with ischemic μFR values (≤0.80) at follow-up. Receiver operating characteristic (ROC) curve analysis demonstrated good predictive performance of post-DCB μFR for detecting follow-up ischemia (AUC = 0.758; 95% CI 0.697–0.812; $p < 0.001$), with no difference between paclitaxel-coated and sirolimus-coated balloons ($p = 0.712$). The optimal post-DCB μFR cut-off predicting follow-up ischemia was μFR ≤ 0.86, yielding an accuracy of 81.1%, sensitivity of 74.4%, specificity of 69.0%, negative predictive value of 92.0%, and positive predictive value of 36.0%. In contrast, the angiographic parameter % diameter stenosis (%DS ≥ 30%) showed no association with follow-up ischemic μFR (AUC = 0.525; 95% CI 0.443–0.605; $p = 0.677$) and performed significantly worse than post-PCI μFR ($p = 0.001$). The overall results of PICCOLETO VI are shown in Fig. 19.2 [24]. A case of DCB-PCI guided by μFR assessment in the setting of a true coronary bifurcation lesion is reported in Fig. 19.3.

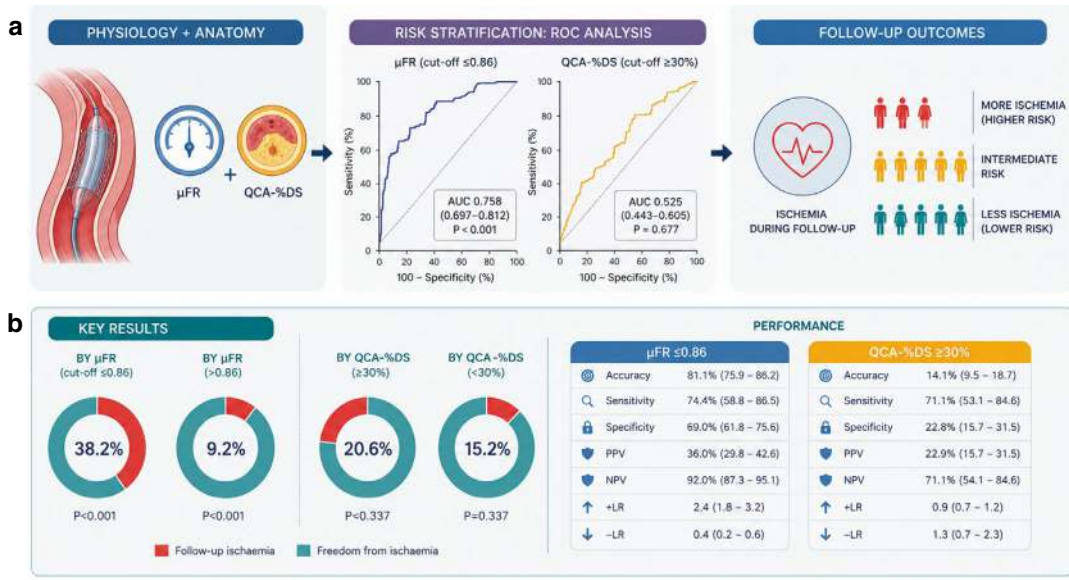


Fig. 19.2 Post-DCB μFR value interaction with follow-up ischemia (μFR ≤ 0.80). Receiver operating characteristic curves for predicting follow-up ischemia. Diagnostic performance of post-DCB μFR (blue) and Quantitative Coronary Angiography %DS (yellow) in predicting follow-up ischemia. Lower panels: Diagnostic performance of post-DCB μFR ≤ 0.86 and Quantitative Coronary Angiography %DS ≥ 30% in predicting follow-up ischemia (red). AUC, area under the curve; DCB, drug coated balloon; DS, degree of stenosis; LR, likelihood ratio; μFR, Murray's law-based QFR; NPV, negative predictive value; PPV, positive predictive value; QCA, Quantitative Coronary Angiography

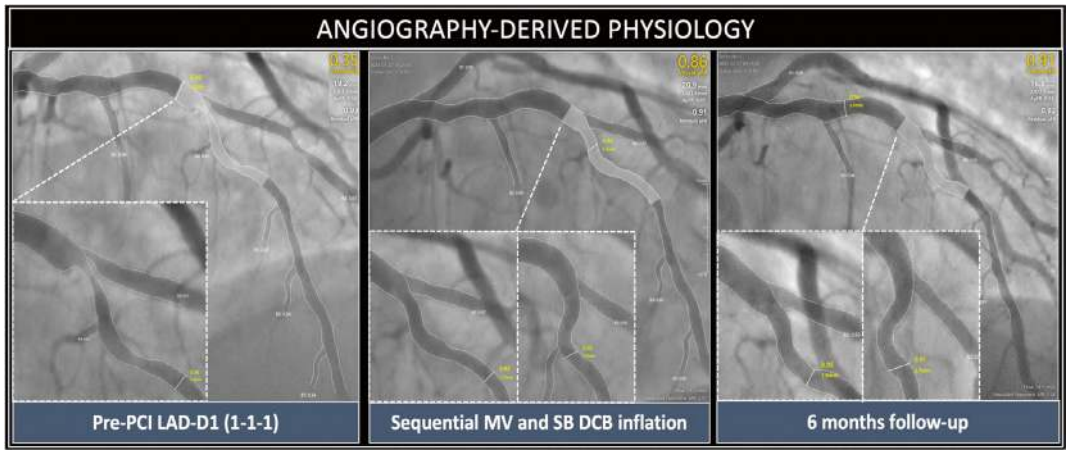


Fig. 19.3 Murray's law-based physiology-guided DCB–only PCI for a true coronary bifurcation lesion in the setting of STEMI. A case of LAD-D1 bifurcation lesion (Medina 1,1,1) with ischemic baseline values of single-view, Murray law–based quantitative flow ratio (μFR) in both the main vessel (MV, μFR = 0.35) and the side branch (SB, μFR = 0.74). After successful wiring of both branches, lesion preparation was performed using a kissing-balloon inflation (KBI) technique with non-compliant balloons. Sequential inflations of paclitaxel-coated drug-coated balloons (DCB) were subsequently carried out in the MV (3.5 × 30 mm) and SB (2.5 × 20 mm), achieving an optimal angiographic and physiological result, with post-procedural μFR values of 0.86 in the MV and 0.97 in the SB. Sustained vessel patency and functional improvement were confirmed at elective follow-up, with μFR values of 0.91 and 0.93, respectively. LAD = left anterior descending coronary artery; MV = main vessel; SB = side branch; PCI = percutaneous coronary intervention; μFR = angiography-derived or Murray law-based quantitative flow ratio

In another observational cohort, Garin et al. reported post-procedural 3D-μQFR was significantly lower in VOCE lesions (median 0.76 vs. 0.90, $p < 0.001$) and ROC analysis identified optimal μQFR threshold of 0.83 (AUC 0.74) [37].

Nonetheless, as spontaneous healing of dissections and positive vessel remodeling may improve physiological indices over time and given the limited and preliminary nature of available data, recent expert consensus does not currently endorse any specific physiological threshold for DCB procedures [10]. Future research is warranted to define evidence-based physiological criteria that can reliably guide lesion preparation, DCB selection, and post-procedural assessment in this evolving field.

All studies evaluating coronary physiology assessment are summarized in Table 19.1.

19.4 Intracoronary Imaging

Over the past years, intracoronary imaging (ICI) has emerged as an essential tool for the guidance of PCI. In complex coronary lesions, ICI guidance has consistently been shown to improve clinical outcomes compared with angiography guidance [38–40]. According to the latest European and American myocardial revascularization guidelines, ICI is strongly recommended (Class I, Level A) in long lesions and other complex scenarios such as left main or bifurcation disease, in order to reduce the risk of cardiac death, target vessel myocardial infarction (MI), TLR, and stent thrombosis [38–40]. Two large network meta-analyses showed that, in aggregate, intracoronary imaging guidance (with either intravascular ultrasound (IVUS) or optical coher-

ence tomography (OCT)) for PCI decreases cardiac death, target vessel MI, target lesion revascularization, and stent thrombosis [41, 42]. Similarly, the OCTOBER trial demonstrated improved outcomes with OCT guidance in bifurcation lesions, including left main bifurcations [43].

While strong evidence supports ICI use after stent implantation, limited data are available on its role following DCB-PCI. ICI provides detailed assessment of vessel size, plaque composition, extent, and morphology, allowing for more optimized lesion preparation compared with angiography alone. The DCB-ARC consensus recommends incorporating ICI to achieve precise vessel sizing, appropriate DCB selection, and better characterization of plaque morphology, all of which may lead to superior angiographic outcomes [10, 44, 45]. In the ULTIMATE III trial, IVUS-guided DCB angioplasty was compared with angiography guidance in 260 HBR patients with de novo lesions. IVUS guidance resulted in greater acute lumen gain, lower late lumen loss (-0.10 ± 0.34 mm vs. 0.03 ± 0.52 mm; $p = 0.025$), and larger minimal lumen diameter with less residual stenosis at 7-month follow-up. Although the study was not powered for clinical outcomes and found no significant difference in target vessel failure, IVUS guidance provided superior angiographic results, supporting its potential role in optimizing DCB angioplasty [46].

In an OCT- and physiology-guided study including 50 de novo lesions, Yamamoto et al. observed that lesions with LLE at follow-up exhibited a lower post-procedural area stenosis after DCB angioplasty (38.8% vs. 52.2%; $p = 0.01$), highlighting the potential prognostic value of early anatomical results for subsequent positive vessel remodeling. Furthermore, intimal fractures with separation of the intima from the media are associated with improved outcomes after DCB-only PCI. This benefit likely reflects the dual effect of controlled dissections, facilitating vascular remodeling and enhancing drug penetration into the vessel wall [47]. However, no evidence-based intravascular imaging criteria for DCB optimization have yet been established and according to a Japanese Clinical Expert Consensus medial dissection, intramural hematoma or extra medial injury should be covered with "bail-out" stenting [48].

All studies investigating intracoronary imaging assessment are summarized in Table 19.2. Figure 19.4 illustrates a case of DCB–PCI guided by physiological and IVUS assessment.

Table 19.2 Overview of intracoronary imaging-guided DCB–PCI studies

Intracoronary imaging				
Study/author	Type of study	Technique/method	Patients/setting	Key findings/main outcomes
Gao et al., ULTIMATE III, JACC: *Cardiovasc Interv* (2024)	Prospective, Multicenter RCT De novo lesions	IVUS-guided vs. angiography-guided DCB-PCI	260 HBR patients with de novo lesions (2–4 mm, ≤15 mm): 130 angio-guided, 130 IVUS-guided	IVUS guidance improved outcomes: – Greater acute lumen gain (1.93 ± 0.54 mm vs. 1.78 ± 0.48 mm, $p = 0.019$) – Lower late lumen loss (Δ 0.14 mm, 95% CI 0.02–0.26; $p = 0.025$)– Higher MLD (2.06 ± 0.62 mm vs. 1.75 ± 0.63 mm, $p < 0.001$) – No significant difference in TVF (3.1% vs. 0.8%, $p = 0.37$).
Yamamoto et al. *Int J Cardiol* (2022)	Prospective observational, single-center De novo lesions	OCT + FFR/iFR	50 de novo lesions (OCT-guided DCB with follow-up) (medium vessels)	Late lumen enlargement (LLE) associated with lower post-DCB OCT % area stenosis (38.5% vs. 45.1%, $p = 0.03$) Dissections linked to positive remodeling (94% healed; 62% with chronic LLE)
Fezzi et al., *European Heart Journal/ EuroIntervention/JACC* (2025) (DCB-ARC Consensus)	International expert consensus	OCT/IVUS		Intravascular imaging enhances vessel sizing, plaque characterization, and DCB selection; standardized imaging criteria for DCB-PCI still lacking.
Muramatsu et al, Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) Consensus, *Cardiovascular Intervention and Therapeutics* (2023)	Expert consensus statement	IVUS/OCT		Medial dissection with hematoma identified by imaging should prompt bail-out stenting; imaging recommended to guide DCB use and optimize outcomes

DCB drug-coated balloon, *FFR* fractional flow reserve, *HBR* high bleeding risk, *IVUS* intravascular ultrasound, *iFR* instantaneous wave-free ratio, *LLE* late lumen enlargement, *MLD* minimal lumen diameter, *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention, *RCT* randomized controlled trial, *TVF* target vessel failure, *%AS* percent area stenosis

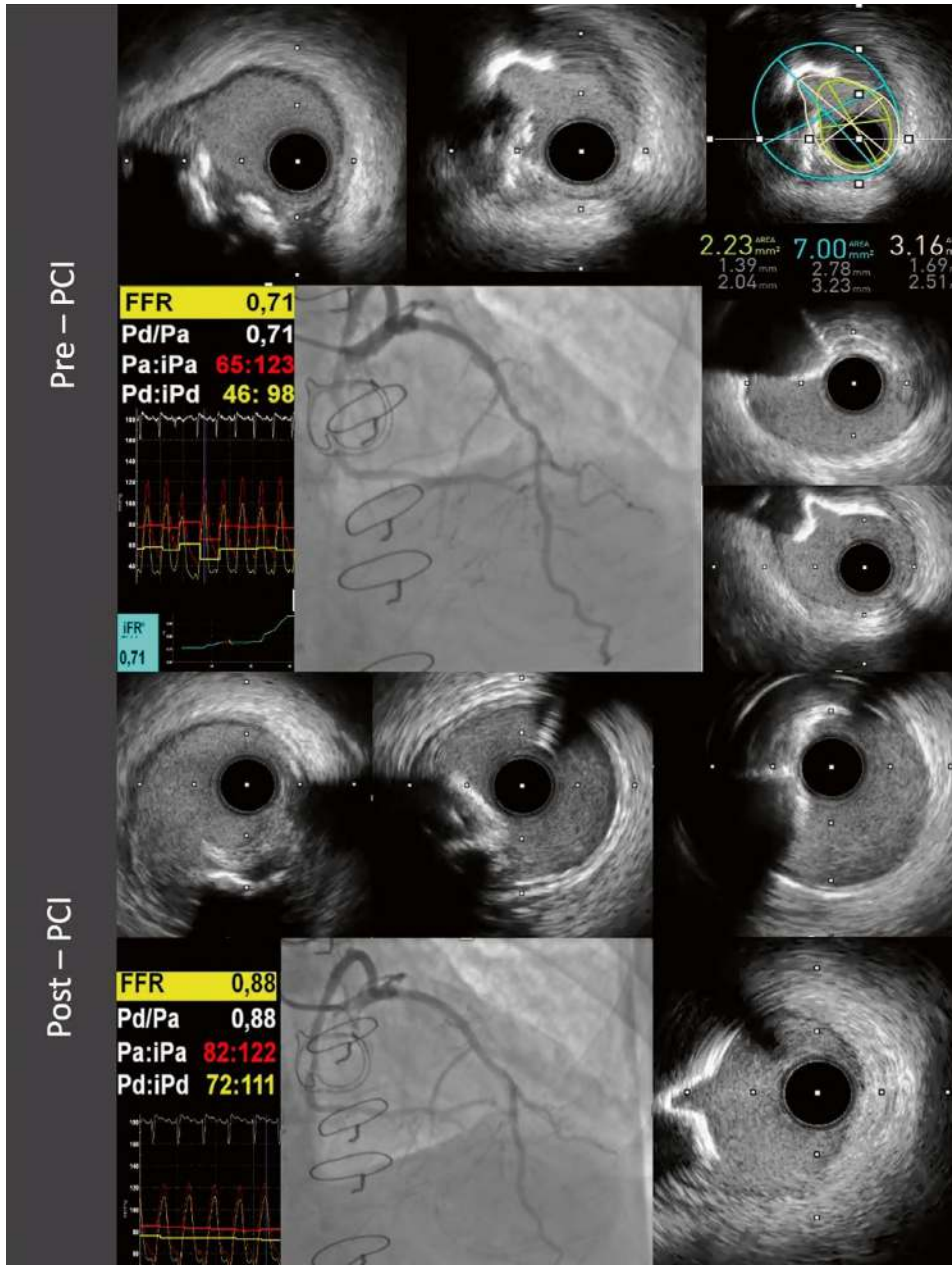


Fig. 19.4 Imaging- and physiology-guided DCB–PCI for a significant calcified stenosis in the mid-LAD. A case of severely calcified mid–LAD stenosis with eruptive nodular calcification and flow-limiting indices at invasive pressure-wire assessment (pre-PCI: iFR = 0.71, FFR = 0.71), and with a functional drop at the iFR pull-back. Lesion preparation included pre-dilatation with a non-compliant balloon (2.5 × 15 mm), intravascular lithotripsy (IVL, 3.0 × 12 mm, 12 cycles), and subsequent optimization with a non-compliant balloon (3.5 × 15 mm). IVUS after lesion preparation confirmed adequate luminal area and visible calcium fractures, indicative of effective plaque modification. A drug-coated balloon (DCB, 3.0 × 30 mm) was then applied to the target segment. Post-procedural physiological reassessment demonstrated normalization of coronary flow (FFR = 0.88), confirming the absence of residual ischemia and a satisfactory functional outcome without stent implantation. FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; PCI = percutaneous coronary intervention; μFR = angiography-derived or Murray law-based quantitative flow ratio

19.5 Combined Computational Technologies

Recent advances in computational imaging have enabled the integration of intracoronary imaging and coronary physiology, allowing virtual, wire-free assessment of hemodynamics directly from OCT or IVUS pullbacks. The optical flow ratio (OFR) derived from OCT and the ultrasonic flow ratio (UFR) from IVUS reconstruct three-dimensional vessel geometry and simulate blood flow using computational fluid dynamics. Both methods show excellent diagnostic accuracy compared with invasive FFR (≈90%), with fast computation times (<2 min) and high reproducibility [49–51].

In this context, combining anatomical and physiological information in a single imaging run may prove particularly valuable for DCB-PCI, where procedural success depends on plaque morphology assessment, optimal lesion preparation and improvement of coronary flow. Beyond estimating pressure-derived indices, these hybrid platforms may now quantify dissection volume and geometry, providing direct insight into their hemodynamic impact. By integrating flow modeling, and dissection volume assessment, computational imaging is poised to advance toward personalized, physiology-driven DCB strategies aimed at improving vessel remodeling and long-term patency (Fig. 19.5).

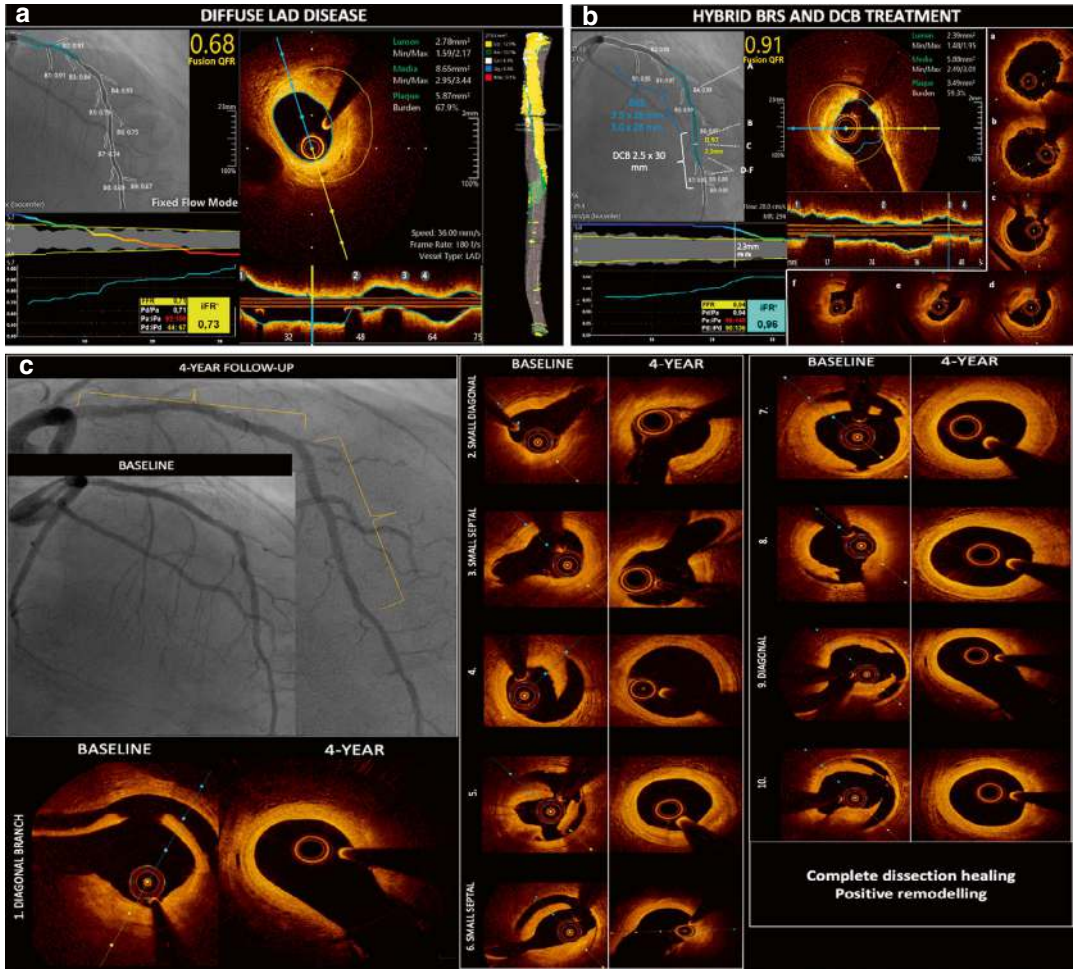


Fig. 19.5 Integrated functional and intravascular imaging assessment after DCB-PCI. (**a**) Diffuse LAD disease with impaired coronary flow (QFR = 0.68, iFR = 0.73, FFR 0.71) and OCT-confirmed high plaque burden. (**b**) Hybrid treatment with BRS and DCB angioplasty was performed restoring physiological parameters (QFR = 0.91, iFR = 0.96, FFR = 0.94) and achieved optimal lumen expansion. Extensive dissection involving the media was confirmed at the OCT analysis after DCB treatment. (**c**) Four-year follow-up showed complete dissection healing and positive vascular remodeling. Integration of QFR and OCT enables precise evaluation of residual ischemia and vessel healing, guiding tailored DCB-PCI strategies. BRS = bioresorbable scaffold; DCB = drug coated balloon; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; PCI = percutaneous coronary intervention; QFR = angiography-derived or Murray Law-based quantitative flow ratio

19.6 Conclusions

The success of DCB-only PCI relies on proper lesion preparation and accurate evaluation of the procedural result. To date, angiography remains the reference standard, and virtually all clinical trials assessing DCB efficacy have relied on angiographic criteria to define procedural success. However, these recommendations are largely based on expert consensus rather than robust prospective evidence, and angiography provides only a limited luminographic assessment of vessel geometry and dissection severity. The integration of coronary physiology and intracoronary imaging offers complementary information to refine procedural evaluation. Pressure-wire- and angiography-derived indices provide functional evidence of flow improvement, whereas IVUS and OCT allow detailed assessment of plaque morphology, vessel sizing, and dissection charac-

teristics. Emerging computational imaging technologies further combine anatomical and physiological data, allowing quantification of dissection volume and flow disturbances. These advances represent a step toward personalized, physiology-guided DCB strategies, aimed at optimizing acute outcomes and promoting long-term vessel healing and patency.

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20 Long-Term Follow-Up Data After DCB Angioplasty: Lessons from RCT and Real-World Studies

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20.1 Introduction

Currently, percutaneous coronary intervention (PCI) is mainly performed using permanent metallic drug-eluting stents (DES), which have well-established safety and efficacy. However, accumulating evidence indicates that over the long term, segments treated with DES have an increased risk of cardiovascular events, presumably due to the permanent presence of a foreign body (metal and/or polymer coating) and the suppression of physiological vasomotion. In contrast, PCI with a drug-coated balloon (DCB) suppresses inflammatory and proliferative tissue responses both acutely and subacutely, while long-term, they allow for vessel remodeling and maintain vasomotion [1, 2].

The theoretical advantages of plain old balloon angioplasty (POBA) were demonstrated in early studies with long-term follow-up. In 1997, Ormiston et al. [3] showed a significant temporal reduction in mean diameter stenosis from 36.3 ± 14.2% at 6 months to 29.6 ± 13.5% at 5 years ($P < 0.0001$) following POBA, with no lesion meeting the criterion for late restenosis. In 2012, Yamaji et al. reported the longest follow-up

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comparing POBA and bare-metal stents (BMS) with outcomes reported at 15–23 years [4]. Although the cumulative incidence of target lesion revascularization (TLR) during the follow-up period was significantly higher after POBA than after BMS implantation (44.6% vs. 36.0%, $P < 0.001$), the incidence of late TLR (>4 years) tended to be lower after POBA (16.3% vs. 21.4%, $p = 0.11$). In addition, the absolute change in late lumen loss between early (6–14 months) and long-term (4–10 years) follow-up was significantly smaller in the POBA group.

Therefore, it is crucial to investigate whether similar observations occur late after DCB treatment. In this chapter, we will focus on the outcomes of DCB treatment beyond 1 year.

20.2 ISR-Long Term Data

DCB was primarily designed to treat in-stent restenosis (ISR), aiming to prevent the implantation of another metal layer in a previously failed stent. Over the past two decades, clinical evidence from randomized trials have established the role of DCB angioplasty in the treatment of ISR. This section summarizes key randomized trials with long-term follow-up data, along with findings from meta-analyses and pooled analyses, and outlines current guideline recommendations on the management of ISR (Table 20.1 and Fig. 20.1).

Table 20.1 Randomized trials with long-term follow-up for BMS-ISR and DES-ISR

Study	Follow up	Publication year	Design	*n*	ISR type	DCB	Comparator	MACE	Mortality	MI	TLR
PACCOCATH-ISR I & II	5 years	2012	RCT, open label	108	BMS-ISR	PCB PACCOCATH	POBA	1 year: 9% vs. 44% ($p = 0.001$) 2 years: 11% vs. 46% ($p = 0.001$) 3 years: 27.8% vs. 59.3% ($p = 0.009$)	1 year: 4% vs. 6% ($p = 0.912$) 2 years: 4% vs. 6% ($p = 0.912$) 5 years: 9.3% vs. 14.8% ($p = 0.938$)	1 year: 2% vs. 9% ($p = 0.577$) 2 years: 2% vs. 9% ($p = 0.577$) 5 years: 9.3% vs. 14.8% ($p = 0.510$)	1 year: 4% vs. 37% ($p = 0.001$) 2 years: 6% vs. 37% ($p = 0.001$) 5 years: 9.3% vs. 38.9% ($p = 0.004$)
PEPCAD II	3 years	2015	RCT, open label	131	BMS-ISR	PCB SeQuent Please	PES Taxus Liberte	1 year: 7.7% vs. 17.4% ($p = 0.11$) 3 years: 9.1% vs. 18.5% ($p = 0.14$)	1 year: 3.1% vs. 4.8% 3 years: 7.6% vs7.7%	1 year: 0% vs. 1.6% 3 years: 1.5% vs. 1.6%	1 year: 6.2% vs. 15.9% 3 years: 6.2% vs. 15.4% ($p = 0.10$)
RIBS V	3 years	2016	RCT, open label	189	BMS-ISR	PCB SeQuent Please	EES Xience Prime	1 year: 8% vs. 6% ($p = 0.60$) 2 years: 10% vs. 8% ($p = 0.81$) 3 years: 12% vs. 10% ($p = 0.64$)	1 year: 4% vs. 0% ($p = 0.31$) 2 years: 6% vs. 1% ($p = 0.04$) 3 years: 7% vs. 2% ($p = 0.08$)	1 year: 3% vs. 4% ($p = 0.68$) 2 years: 4% vs. 5% ($p = 0.72$) 3 years: 4% vs. 5% ($p = 0.72$)	1 year: 6% vs. 1% ($p = 0.09$) 2 years: 6% vs. 2% ($p = 0.13$) 3 years: 8% vs. 2% ($p = 0.04$)

(continued)

Table 20.1 (continued)

Study	Follow up	Publication year	Design	*n*	ISR type	DCB	Comparator	MACE	Mortality	MI	TLR
TIS	3 years	2018	RCT, open label	136	BMS-ISR	PCB SeQuent please	EES Promus element	1 year: 10.3% vs. 19.1% ($p = 0.213$) 3 years: 19.1% vs. 29.4% ($p = 0.230$)	1 year: 1.5% vs. 1.5% ($p > 0.999$) 3 years: 8.8% vs. 8.8% ($p > 0.999$)	1 year: 1.5% vs. 1.5% ($p > 0.999$) 3 years: 4.4% vs. 4.8% ($p > 0.999$)	1 year TVR: 7.4% vs. 16.2% ($p = 0.110$) 3 years TVR: 12.9% vs. 22.2% ($p = 0.205$)
PEPCAD-DES	3 years	2015	RCT, open label	110	DES-ISR	PCB SeQuent please	POBA	0.5 years: 16.8% vs. 50.0% ($p < 0.001$) 1 year: 16.8% vs. 52.6% ($p < 0.001$) 3 years: 20.8% vs. 52.6% ($p = 0.001$)	0.5 years: 1.4% vs. 13.2% ($p = 0.010$) 1 year:1.4% vs. 13.2% ($p = 0.010$) 3 years: 8.3% vs. 13.2% ($p = 0.423$)	0.5 years: 0% vs. 2.6% ($p = 0.167$) 1 year: 0% vs. 5.3% ($p = 0.049$) 3 years: 0% vs. 5.3% ($p = 0.049$)	0.5 years: 15.3% vs. 36.8% ($p = 0.010$) 1 year: 15.3% vs. 36.8% ($p = 0.010$) 3 years: 19.4% vs. 36.8% ($p = 0.046$)
PEPCAD CHINA ISR	2 years	2016	RCT, open label	220	DES-ISR	PCB SeQuent please	PES Taxus Liberte	1 year TLF: 16.5% vs. 16.0% ($p = 0.92$) 2 years TLF: 16.8% vs. 18.6% ($p = 0.73$)	1 year: 0% vs. 1.9% ($p = 0.24$) 2 years: 0% vs. 4.9% ($p = 0.03$)	1 year: 3.7% vs. 6.6% ($p = 0.33$) 2 years: 3.7% vs. 6.9% ($p = 0.31$)	1 year: 15.6% vs. 12.3% ($p = 0.48$) 2 years: 15.9% vs. 13.7% ($p = 0.66$)

ISAR-DESIRE 3	3 years 10 years	2015, 2024	RCT, open label	402	DES- ISR	PCB SeQuent please	PES Taxus Liberte, POBA	1 year: 23.5% vs. 19.3% vs. 46.2% 3 years: 38.0% vs. 37.7% vs. 55.7% 5 years: 40.2% vs. 41.6% vs. 56.8% ($p < 0.001$) 10 years: 55.9% vs. 62.4% vs. 72.0% ($p < 0.001$)	1 year: 2.2% vs. 4.6% vs. 5.3% 3 years: 6.0% vs. 15.3% vs. 9.4% 5 years: 9.3% vs. 20.9% vs. 20.0% ($p = 0.024$) 10 years: 35.7% vs. 47.2% vs. 38.7% ($p = 0.145$)	1 year: 2.1% vs. 2.4% vs. 1.5% 3 years: 5.4% vs. 3.2% vs. 1.5% 5 years: 5.3% vs. 5.3% vs. 4.3% ($p = 0.881$) 10 years: 9.8% vs. 5.3% vs. 6.6% ($p = 0.555$)	1 year: 22.1% vs. 13.5% vs. 43.5% 3 years: 33.3% vs. 24.2% vs. 50.8% 5 years: 36.5% vs. 29.2% vs. 50.6% ($p < 0.001$) 10 years: 44% vs. 39% vs. 58% ($p < 0.001$)
RIBS IV	3 years	2018	RCT, open label	309	DES- ISR	PCB SeQuent please	EES Xience prime	1 year: 15.6% vs. 6.5% ($p = 0.009$) 2 years: 17.5% vs. 8.4% ($p = 0.015$) 3 years: 20.1% vs. 12.3% ($p = 0.04$)	1 year: 1.9% vs. 2.6% ($p = 0.71$) 2 years: 4.5% vs. 3.9% ($p = 0.77$) 3 years: 7.8% vs. 7.1% ($p = 0.82$)	1 year: 3.2% vs. 1.3% ($p = 0.24$) 2 years: 3.2% vs. 2.6% ($p = 0.73$) 3 years: 4.5% vs. 2.6% ($p = 0.35$)	1 year: 13.0% vs. 4.5% ($p = 0.007$) 2 years: 14.9% vs. 5.2% ($p = 0.003$) 3 years: 15.6% vs. 7.1% ($p = 0.015$)

BMS bare-metal stent, *DCB* drug-coated balloon, *DES* drug-eluting stent, *EES* everolimus-eluting stent, *ISR* in-stent restenosis, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *PCB* paclitaxel-coated balloon, *PES* paclitaxel-eluting stent, *POBA* plain old balloon angioplasty, *RCT* randomized controlled trial, *TLR* target lesion revascularization

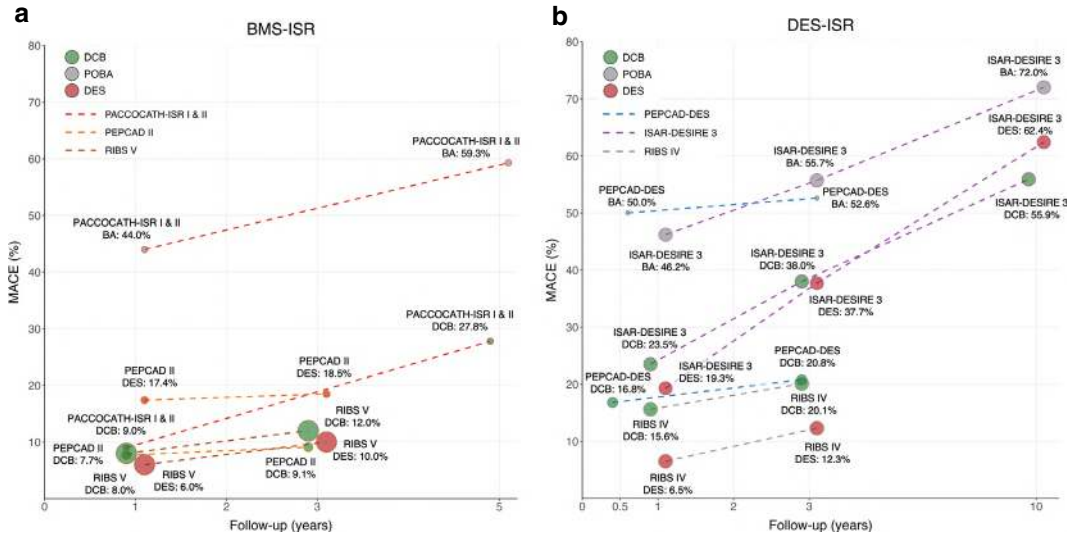


Fig. 20.1 Randomized trials with long-term follow-up for BMS-ISR and DES-ISR. (**a**) BMS-ISR. (**b**) DES-ISR. *BMS* bare-metal stent, *DCB* drug-coated balloon, *DES* drug-eluting stent, *ISR* in-stent restenosis, *MACE* major adverse cardiovascular events, *POBA* plain old balloon angioplasty

20.3 BMS-ISR

20.3.1 PACCOCATH-ISR I/II (5 Year) [5]

The PACCOCATH-ISR I and II trials were first-in-human, randomized, double-blind, multicenter studies evaluating a paclitaxel-coated balloon (PCB) versus an uncoated balloon for the treatment of ISR (BMS: 96%, DES: 4%) in 108 patients. At 5-year follow-up, major adverse cardiovascular events (MACE) were significantly lower in the DCB arm (27.8% vs. 59.3%; $p = 0.009$), driven primarily by a marked reduction in TLR (9.3% vs. 38.9%; $p = 0.004$). These studies demonstrated the superiority of DCB angioplasty over POBA for the treatment of BMS-ISR.

20.3.2 PEPCAD II (3 Years) [6]

The PEPCAD II trial provided additional randomized evidence supporting the long-term efficacy of PCB in treating BMS-ISR. In this study, 131 patients with BMS-ISR were randomized to receive either a PCB (SeQuent Please, B. Braun, Germany) or a paclitaxel-eluting stent (PES: TAXUS Liberté, Boston Scientific, USA). The respective lesion-related MACE rates were 7.6% vs. 16.9% ($p = 0.11$) at 12 months and 9.1% vs. 18.5% ($p = 0.14$) at 36 months, with the differences mainly driven by a lower TLR rate (6.2% vs. 15.4%; $p = 0.10$). Between 12 and 36 months, no deaths or additional TLR events occurred in either group. These results indicate that in BMS-ISR, PCB angioplasty provides long-term clinical outcomes comparable to those of PES implantation.

20.3.3 RIBS V (3 Years) [7]

The RIBS V trial provided a contemporary comparison between PCB (SeQuent Please) and everolimus-eluting stents (EES: Xience Prime, Abbott Vascular, USA) in patients with BMS-ISR. A total of 189 patients were randomized, and complete follow-up was obtained in all par-

ticipants at 1, 2, and 3 years. At 3 years, rates of cardiac death (2% vs. 1%), myocardial infarction (MI) (4% vs. 5%), and target-vessel revascularization (TVR) (9% vs. 5%) were similar between groups, whereas TLR was significantly lower with EES (2% vs. 8%; $p = 0.04$). Late (>1 year) revascularization events and stent thrombosis were rare and comparable in both arms. In patients with BMS-ISR, RIBS V demonstrated comparable safety between PCB and EES, while EES was associated with a lower incidence of TLR.

20.4 DES-ISR

20.4.1 PEPCAD-DES (3 Years) [8]

The PEPCAD-DES trial extended the evidence for DCB therapy to the setting of DES-ISR. This multicenter, randomized, single-blind study enrolled 110 patients with DES-ISR and compared PCB (SeQuent Please) angioplasty with POBA. Approximately half of the lesions in both groups contained multiple stent layers, reflecting the real-world complexity of restenosis. At 3-year follow-up, PCB angioplasty demonstrated significantly lower rates of TLR (19.4% vs. 36.8%; $p = 0.046$) and MACE (20.8% vs. 52.6%; $p = 0.001$) compared with POBA, with no evidence of late catch-up. In addition, repeat TLR events were markedly reduced with PCB (1.4% vs. 13.2%; $p = 0.021$). These findings demonstrate that PCB angioplasty is superior to POBA for the treatment of DES-ISR, with durable efficacy and safety maintained through 3 years.

20.4.2 ISAR-DESIRE 3 (10 Years) [9]

The ISAR-DESIRE 3 trial represents the longest available randomized follow-up in patients with DES-ISR, providing important insights into the long-term durability of DCB therapy. In this three-arm study, 402 patients were randomized to POBA, PCB (SeQuent Please), or PES (TAXUS Liberté), with clinical follow-up extending to 10 years. The primary endpoint, a composite of cardiac death, target-vessel MI (TV-MI), target-lesion thrombosis, or TLR, occurred in 72.0%, 55.9%, and 62.4% of patients treated with POBA, PCB and PES, respectively ($p < 0.001$). There was no significant difference in a pairwise comparison between PCB and PES (HR 1.10; 95% CI 0.79–1.52), with both strategies markedly outperforming POBA. Rates of TLR were lower with PCB and PES than with POBA (43.9% vs. 38.6% vs. 58.0%; $p < 0.0001$). In the first 5 years, an early excess of all-cause and cardiac mortality was observed with PES compared with PCB, although this difference diminished with longer follow-up. The 10-year follow-up of ISAR-DESIRE 3 demonstrated that in DES-ISR, both PCB and PES remained superior to POBA in efficacy and safety, with sustained and comparable long-term performance.

20.4.3 RIBS IV (3 Years) [10]

The RIBS IV trial is a prospective randomized trial comparing PCB (SeQuent Please) with EES (Xience Prime) in patients with DES-ISR. A total of 309 patients were randomized, and clinical follow-up was available in all participants at 3 years. The composite endpoint of cardiac death, MI, and TLR occurred less frequently with EES (12.3% vs. 20.1%; $p = 0.04$), mainly driven by a lower TLR (7.1% vs. 15.6%; $p = 0.015$). Rates of cardiac death (3.9% vs. 3.2%), MI (2.6% vs. 4.5%), and stent thrombosis (1.3% vs. 2.6%) were comparable in both arms. The 3-year clinical follow-up of RIBS IV demonstrated that in patients with DES-ISR, EES reduces the need for repeat interventions compared with PCB.

20.5 Meta-analysis and Pooled Analysis

20.5.1 Meta-analysis—DCB vs. EES (1–3 Years) [11]

A meta-analysis by Elgendy et al. pooled data from five randomized trials (n = 962) directly comparing DCB with EES for the treatment of both BMS-ISR and DES-ISR, including RIBS V and RIBS IV. At a mean angiographic follow-up of 8.6 months, DCB was associated with a smaller in-segment minimal lumen diameter (standardized mean difference −0.24; 95% CI −0.46 to −0.01). While there was no significant difference in TVR at 1 year (RR 1.15; 95% CI 0.60–2.19), the risk of TVR at 3 years (RR 1.87; 95% CI 1.15–3.03) and TLR (RR 2.17; 95% CI 1.13–4.19) at 2 years was significantly higher with DCB. There were no differences in MI, stent thrombosis, or mortality. In summary, long-term safety outcomes were comparable between DCB and EES, whereas rates of TLR and TVR were significantly lower with EES.

20.5.2 DAEDALUS Study—Pooled Analysis (3 Years) [12]

The DAEDALUS study is a large individual patient-level pooled analysis directly comparing DCB angioplasty with repeat DES implantation for the treatment of ISR. This analysis included 1958 patients (BMS-ISR n = 710, DES-ISR n = 1248) across 10 randomized trials, with clinical follow-up extended to 3 years. In BMS-ISR, there was no significant difference between DCB and DES in either the primary efficacy endpoint of TLR (9.2% vs. 10.2%; HR 0.83, 95% CI 0.51–1.37) or the primary safety endpoint of death, MI, or target lesion thrombosis (8.7% vs. 7.5%; HR 1.13, 95% CI 0.65–1.96). In contrast, in DES-ISR, DCB angioplasty was associated with a higher rate of TLR (20.3% vs. 13.4%; HR 1.58, 95% CI 1.16–2.13), but a numerically lower composite safety endpoint (9.5% vs. 13.3%; HR 0.69, 95% CI 0.47–1.00). Regardless of treatment, DES-ISR had a substantially higher overall TLR risk than BMS-ISR (HR 0.56; 95% CI 0.42–0.74). In summary, at 3-year follow-up, the DAEDALUS study demonstrated that DCB angioplasty and DES implantation are similarly effective and safe in the treatment of BMS-ISR. In contrast, in DES-ISR, DCB angioplasty is significantly less effective than repeat DES implantation and is associated with a non-significant reduction in the primary composite safety endpoint.

20.6 Summary—ISR

The early randomized trials and meta-analyses prompted the 2018 ESC Guidelines for myocardial revascularization to recommend DCB for the treatment of BMS-ISR and DES-ISR (Class I, Level A) [13]. Contemporary evidence from meta-analyses comparing PCB with EES, and the results of the DAEDALUS pooled analysis, resulted in the 2024 ESC Guidelines for Chronic Coronary Syndrome (CCS) being updated to recommend DES over DCB for the treatment of DES-ISR (Class I, Level A), with the previous reference to BMS-ISR removed [14].

Notably, the evidence supporting this recommendation remains limited. Most trials underpinning the latest guideline update had low rates of intravascular imaging use, restricting the ability to identify the underlying mechanisms of the ISR, such as whether it was due to stent under-expansion or under-sizing. If intravascular imaging-guided assessment and appropriate lesion preparation had been performed, long-term outcomes might have improved. Moreover, ISR encompasses a wide range of pathologies, and optical coherence tomography (OCT) can identify distinct neointimal tissue characteristics that may influence the response to specific treatment strategies. Homogeneous patterns, typically rich in smooth muscle cells, may be particularly amenable to DCB treatment, whereas non-homogeneous patterns (heterogeneous or layered), associated with extracellular matrix, proteoglycans, organized fibrin, or neoatherosclerosis, may be better treated with DES rather than DCB [15, 16]. Irrespective of the tissue pattern, implanting an additional DES introduces

potential risks, including late stent thrombosis, neoatherosclerosis, and adverse long-term outcomes due to multiple metal layers.

The ongoing ISAR-DESIRE 5 trial (NCT05544864) [17] was designed to determine whether the morphology of ISR, as defined by OCT, impacts the treatment effect of DES versus DCB. In the study, 376 patients with DES-ISR will be stratified according to the ISR pattern observed on OCT (homogeneous vs. non-homogeneous) and randomized 1:1 to receive either a DES or DCB, with the primary endpoint being MACE at 24 months. This trial is expected to provide new insights into how OCT-defined ISR tissue patterns may guide the selection of DES versus DCB, and how such a tailored approach may influence long-term clinical outcomes.

20.7 De Novo Small-Vessel Disease-Long Term Data

In small-vessel disease (SVD, reference vessel diameter [RVD] <3.0 mm), PCI with DES is negatively affected by the inverse relationship between RVD and restenosis risk, resulting in a higher incidence of target lesion failure (TLF) compared with PCI in non-SVD [18]. DCB offer a stent-free approach, which is especially beneficial in this context. Notably, PCB angioplasty has been associated with comparable clinical outcomes to those of DES implantation in this population. This section reviews randomized trials comparing PCB angioplasty with DES implantation in de novo SVD, focusing on those with long-term follow-up data (Table 20.2 and Fig. 20.2).

20.7.1 BELLO (3 Years) [19]

The BELLO trial randomized 182 patients with de novo SVD (RVD <2.8 mm by visual estimation, lesion length <25 mm) from 15 Italian centers, in a 1:1 ratio, to receive PCB (In.Pact Falcon, Medtronic, USA) with provisional bare-metal stenting or PES (Taxus Liberté). At 3-year follow-up, the incidence of MACE, defined as all-cause death, MI, or TVR, was significantly lower with PCB angioplasty compared with PES implantation (14.4% vs. 30.4%, $p = 0.015$). The incidence of TLR (6.7% vs. 13.0%, $p = 0.14$) and TVR (3.3% vs. 6.5%, $p = 0.32$) were numerically lower with PCB. There were no cases of target stent or vessel thrombosis in either group. These findings suggest that PCB angioplasty is an effective strategy for de novo SVD, with favorable long-term outcomes compared with PES implantation.

20.7.2 BASKET-SMALL 2 (3 Years) [20]

In the BASKET-SMALL 2 trial, 758 patients with de novo SVD (RVD <3.0 mm) were randomized to PCB (SeQuent Please) or a second-generation DES (EES or PES). The trial, which enrolled patients from 14 centers in Germany, Switzerland, and Austria, is the largest randomized study to evaluate DCB therapy in this setting. Dual antiplatelet therapy (DAPT) was recommended for only one month after DCB, and for 6–12 months after DES implantation, depending on clinical presentation. At 3 years, MACE, comprising cardiac death, non-fatal MI, and TVR, occurred in 15% of patients in both groups ($p = 0.95$). Rates of stent thrombosis (1% vs. 2%) and major bleeding (2% vs. 4%) were numerically lower with PCB versus DES. Despite 72% of patients in the DES arm receiving EES, PCB angioplasty demonstrated comparable long-term efficacy and safety in treating de novo SVD.

20.7.3 RESTORE SVD China (3 Years) [21]

The RESTORE SVD China trial evaluated the performance of the Restore PCB (Cardionovum, Germany) versus the second-generation Resolute Integrity zotarolimus-eluting stent (Medtronic, USA). A total of 230 patients were randomized (RVD ≥2.25 mm and ≤2.75 mm), with an additional 30 very-SVD cases (RVD ≥2.00 mm and <2.25 mm) included in a parallel registry. At 3 years, TLF occurred in 6.1% of

Table 20.2 Randomized trials and observational studies with long-term follow-up for de novo lesions

Study	Follow up	Publication year	Design	*n*	Population	Reference vessel	DCB	Comparator	MACE	Death	MI	TLR
BELLO	3 years	2015	RCT, open label	182	Small vessel (<2.8 mm)	DCB: 2.15 mm, DES: 2.25 mm	PCB IN.PACT FALCON	PES Taxus Liberte	0.5 years: 10.0% vs. 16.3% ($p = 0.21$) 3 years: 14.4% vs. 30.4% ($p = 0.015$)	0.5 years: 1.1% vs. 1.1% ($p = 0.99$)	0.5 years: 1.1% vs. 5.5% ($p = 0.10$)	0.5 years: 4.4% vs. 7.6% ($p = 0.37$) 3 years: 6.7% vs. 13% ($p = 0.14$)
BASKET-SMALL 2	3 years	2020	RCT, open label	758	Small vessel (<3.0 mm)	DCB: 2.75 mm, DES: 2.57 mm	PCB SeQuent please	EES Xience PES Taxus element	1 year: 7% vs. 8% 2 years: 11% v 11% 3 years: 15% vs. 15% ($p = 0.95$)	1 year: 5% vs. 2% 2 years: 6% vs. 5% 3 years: 8% vs. 8% ($p = 0.87$)	1 year: 2% vs. 4% 2 years: 4% vs. 5% 3 years: 6% vs. 6% ($p = 0.52$)	1 year TVR: 4% vs. 5% 2 years TVR: 6% vs. 7% 3 years TVR: 9% vs. 9% ($p = 0.83$)
RESTORE SVD China	3 years	2020	RCT, open label	230	Small vessel (2.25–2.75 mm)	DCB: 2.11 mm, DES: 2.21 mm	PCB Restore	ZES resolute integrity	1 year TLF: 4.4% vs. 2.6% ($p = 0.72$) 2 years TLF: 5.2% vs. 3.7% ($p = 0.75$) 3 years TLF: 6.1% vs. 5.5% ($p = 0.83$)	1 year: 0% vs. 0% (p = NS)	1 year: 0.9% vs. 0% ($p = 0.99$)	1 year: 4.4% vs. 2.6% ($p = 0.72$) 2 years: 5.2% vs. 2.8% ($p = 0.50$) 3 years: 6.1% vs. 2.7% ($p = 0.33$)
PICCOLETO II	3 years	2023	RCT, open label	232	Small vessel (2.0–2.75 mm)	DCB: 2.23 mm, DES: 2.18 mm	PCB Elutax SV	EES Xience	1 year: 5.6% vs. 7.5% ($p = 0.55$) 3 years: 10.8% vs. 20.8% ($p = 0.046$)	1 year: 0% vs. 0.9% ($p = 0.78$) 3 years: 3.9% vs. 4.0% ($p = 0.98$)	1 year: 1.9% vs. 4.7% ($p = 0.23$) 3 years: 2.0% vs. 6.9% ($p = 0.14$)	1 year: 5.6% vs. 5.6% ($p = 0.80$) 3 years: 8.8% vs. 14.8% ($p = 0.18$)

REC CAGEFREE I	3 years	2025	RCT, open label	2272	All size vessel	DCB: 2.74 mm DES: 2.82 mm	PCB Swide	SES Firebird2	2 years DoCE: 6.4% vs. 3.4% ($p = 0.0008$) 3 years DoCE: 8.2% vs. 5.0% ($p = 0.002$)	2 years 3.3% vs. 2.0% ($p = 0.064$) 3 years: 4.3% vs. 3.4% ($p = 0.269$)	2 years: 2.1% vs. 2.0% ($p = 0.97$) 3 years: 2.2% vs. 2.3% ($p = 0.900$)	2 years CPI-TLR: 3.1% vs. 1.2% ($p = 0.0021$) 3 years CPI-TLR: 4.2% vs. 1.6% ($p < 0.001$)
REC CAGEFREE I Small vessel	3 years	2025	RCT, open label	1032	Small vessel (<3.0 mm)	–	PCB Swide	SES Firebird2	2 years DoCE: 5.1% vs. 4.4% ($p = 0.59$) 3 years DoCE: 7.0% vs. 5.8% ($p = 0.440$)			
Hu et al.	2 years	2022	Prospective, multicenter, single arm	119	Large vessel (≥2.75 mm)	DCB: 3.1 mm	PCB SeQuent please PCB Swide	–	TLF 4.2%	0%	0.8%	3.4%
Nakamura et al.	DCB: 1536 days DES: 1343 days	2023	Retrospective, single center	154	Large vessel (≥2.75 mm)	DCB: 2.98 mm, DES: 3.28 mm	PCB SeQuent please	DES	TLF: 6.8% vs. 14.8% ($p = 0.115$)	5.5% vs. 14.8% ($p = 0.058$)	0% vs. 0% ($p = 1.000$)	0% vs. 3.7% ($p = 0.097$)
Merinopoulous et al.	DCB: 3.7 years, DES 3.6 years	2023	Retrospective, single center, PS-matching	1237	All size vessel, stable angina	DCB: 3.0 mm, DES: 3.5 mm	PCB	DES (2nd-generation)		6.4% vs. 8.5% ($p = 0.24$)		
Merinopoulous et al.	DCB: 2.9 years, DES 3.4 years	2023	Retrospective, single center, PS-matching	1139	All size vessel, STEMI	DCB: 3.5 mm, DES: 3.5 mm	PCB	DES (2nd-generation)		10.8% vs. 9.0% ($p = 0.18$)		
REVELATION	5 years	2024	RCT, open label, single center	120	All size vessel, STEMI	DCB: 3.28 mm, DES: 3.20 mm	PCB Pantera lux	SES Orsiro	5.4% vs. 3.9% ($p = 0.720$)			3.6% vs. 2.0%
SPARTAN-LMS	33 months	2023	Retrospective, single center, PS-matching	148	All size vessel, left main true bifurcation	DCB: 3.84 mm, DES: 4.33 mm	PCB SeQuent please	DES (2nd-generation)		19.5% vs. 15.9% ($p = 0.42$)	TVMI: 0% vs. 6.5%	7.3% vs. 8.3% ($p = 0.86$)

BMS bare-metal stent, *CPI-TLR* clinically and physiologically indicated target lesion revascularization, *DCB* drug-coated balloon, *DES* drug-eluting stent, *DoCE* device-oriented composite endpoint, *EES* everolimus-eluting stent, *ISR* in-stent restenosis, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *PCB* paclitaxel-coated balloon, *PES* paclitaxel-eluting stent, *POBA* plain old balloon angioplasty, *PS* propensity score, *RCT* randomized controlled trial, *SES* sirolimus-eluting stent, *STEMI* ST-segment elevation myocardial infarction, *TLF* target lesion failure, *TLR* target lesion revascularization, *TVR* target vessel revascularization, *ZES* zotarolimus-eluting stent

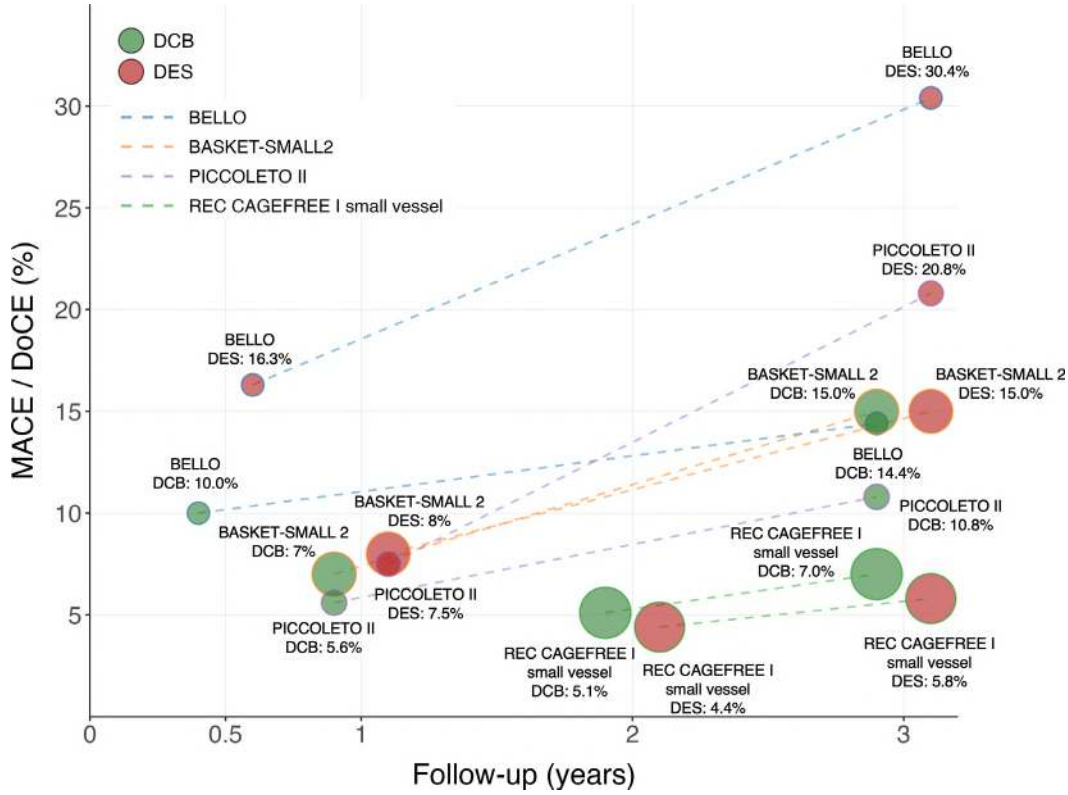


Fig. 20.2 Randomized trials with long-term follow-up for de novo small-vessel disease. *DCB* drug-coated balloon, *DES* drug-eluting stent, *DoCE* device-oriented composite endpoint, *MACE* major adverse cardiovascular events, *POBA* plain old balloon angioplasty

patients in the DCB arm and 5.5% in the DES arm (p = 0.83), with no indication of a "late catch-up" phenomenon. In the very-SVD cohort, the TLF rate was 6.5%. TLR rates remained low and similar across follow-up intervals up to 3 years. Clinical outcomes were likewise favorable in the very-SVD subset. These findings suggest that DCB angioplasty provides sustained clinical safety and efficacy comparable to second-generation DES in SVD, extending to vessels with an RVD close to 2.0 mm.

20.7.4 PICCOLETO II (3 Years) [22]

The PICCOLETO II trial was an investigator-initiated, international study that randomized 232 patients with de novo SVD to a new-generation PCB (Elutax SV, Aachen Resonance, Germany) or an EES (Xience, Abbott Vascular, USA). At 3 years, the cumulative rate of MACE was significantly lower in the DCB arm than in the DES arm (10.8% vs. 20.8%; p = 0.046). Although the individual rates of death, MI, and TLR were similar between groups, acute vessel occlusion only occurred in the DES group (4% vs. 0%; p = 0.042). These findings indicate that in de novo SVD, DCB angioplasty provides a durable, safe, and effective alternative to second-generation DES, supporting the "leave nothing behind" paradigm in SVD PCI.

20.7.5 ANDROMEDA [23]

The ANDROMEDA meta-analysis integrated individual patient-level data from three randomized trials (BELLO, BASKET-SMALL 2, and

PICCOLETO II) to assess the long-term comparative efficacy of PCB angioplasty and DES implantation in de novo SVD. Among 1154 patients followed for 3 years, PCB angioplasty was associated with a significant reduction in the primary endpoint MACE (HR 0.67, 95% CI 0.47–0.96), mainly due to lower MIs and TVR. In a landmark analysis, the risk of MACE between groups remained consistent over time. At 3 years, TLF did not differ significantly between the PCB and DES groups. These results remained consistent in a sensitivity analysis that incorporated reconstructed time-to-event data from a fourth trial (RESTORE SVD China), with similar TLF (HR 0.87, 95% CI 0.63–1.20). In addition, when comparing PCB with second-generation DES, no significant difference in 3-year TLF was observed (HR 1.03, 95% CI 0.70–1.50). The findings underscore the durability of DCB angioplasty and support its role as a viable alternative to DES in the management of SVD.

20.7.6 REC-CAGEFREE I Subgroup Analysis [24]

In the REC-CAGEFREE I trial, a total of 1032 of 2262 randomized patients (45.6%) had SVD, defined as the use of a device with a diameter <3.0 mm. At 3 years, the device-oriented composite endpoint (DoCE: cardiovascular death, TV-MI, or clinically and physiologically indicated TLR [CPI-TLR]) occurred in 37 patients (7.0%) treated with a DCB and in 29 (5.8%) treated with a DES (HR 1.21, 95% CI 0.75–1.97; p = 0.44). These findings suggest that within the small-vessel subset, DCB angioplasty provides long-term outcomes comparable to DES implantation.

20.8 Summary—De Novo Small-Vessel Disease

Evidence from randomized trials and meta-analyses supports the use of DCB as a reasonable and effective treatment option for de novo SVD. Notably, whilst the 2024 ESC CCS guidelines did not include a specific recommendation for the use of DCB in this setting [14], emerging long-term data from ANDROMEDA and results from ongoing randomized trials may influence future guideline updates. TRANSFORM II (NCT04893291) and SELUTION 4 IDE (NCT05946629) are ongoing randomized studies comparing sirolimus-coated balloons with DES for the treatment of de novo lesions (TRANSFORM II up to 3.5 mm), and both will report clinical outcomes out to 5 years. SELUTION 4 IDE study results have been presented in 2025 but not published yet, and subanalyses in the SVD setting are not available yet.

20.9 De Novo Large-Vessel Disease

While long-term evidence supports DCB use for treating ISR and de novo SVD, their role in de novo large-vessel disease remains uncertain. This section summarizes current evidence from observational studies with follow-up beyond one year, comparing DCB-based strategies with contemporary DES (Table 20.2).

Emerging evidence indicates that using DCB for de novo lesions in large vessels is both feasible and clinically effective. A prospective multicenter observational study by Hu et al. in 119 patients with large vessel lesions (RVD ≥2.75 mm) demonstrated favorable mid-term outcomes using a DCB-only strategy, reporting a 2-year TLR rate of only 4.2% [25]. A single-center retrospective study by Nakamura et al. in de novo large vessel lesions (RVD ≥2.75 mm) compared PCB angioplasty (n = 73) to DES (n = 81), and reported similar rates of TLR (6.8% vs. 14.6%, p = 0.097) at approximately 4 years of follow-up [26]. Merinopoulos et al. reported two retrospective analyses from a larger single-center cohort that included vessels of all sizes but predominantly large-vessel lesions (median RVD ≥3.0 mm). Outcomes in the 1237 patients with CCS who received either paclitaxel DCB angioplasty or second-generation DES implantation were reported at a median follow-up of 3.7 years in the DCB group and 3.6 years in the DES group [27]. All-cause mortality occurred in 35 of 544

patients (6.4%) treated with DCB and 59 of 693 (8.5%) treated with DES (HR 1.28, 95% CI 0.84–1.95; $p = 0.24$), with this finding consistent after propensity score matching. Another analysis of the same cohort, but this time in the 1139 patients presenting with ST-segment elevation MI (STEMI), reported outcomes at a median follow-up of 2.9 years for the DCB group and 3.4 years for the DES group [28]. All-cause mortality occurred in 49 of 452 patients (10.8%) treated with DCB and 62 of 687 (9.0%) treated with DES (HR 0.77, 95% CI 0.53–1.12; $p = 0.18$). As in the CCS cohort, these findings remained unchanged after propensity score matching.

The REVELATION trial provides the longest prospective randomized evidence to date evaluating a DCB-only strategy in the setting of primary PCI for STEMI [29]. In this study, 120 patients with de novo culprit lesions suitable for predilatation were randomized to DCB angioplasty or second-generation DES, with bailout stenting required in 18% of the DCB group. At 9 months, fractional flow reserve (FFR) and late lumen loss were similar between the two strategies, whilst at 5-year follow-up, MACE rates were low and comparable (5.4% for DCB vs. 3.9% for DES; $p = 0.72$). Importantly, events occurring between years 2 and 5 were predominantly stent-related, including a recurrent TV-MI due to thrombotic occlusion adjacent to the index stent. These findings highlight the long-term safety of a "leave nothing behind" approach in STEMI patients.

The single-center retrospective SPARTAN LMS study evaluated the safety of DCB angioplasty in 148 patients with de novo unprotected left main stem (LMS) disease [30]. After exclusion of three cases treated with both DCB and DES, paclitaxel DCB angioplasty was compared with second-generation DES over a median follow-up of 33 months. The DCB group contained a significantly greater proportion of true bifurcations (73.2% vs. 48.6%, $p = 0.006$). Rates of all-cause mortality (19.5% vs. 15.9%, $p = 0.42$), cardiac mortality (4.9% vs. 6.5%, $p = 0.786$), TV-MI (0% vs. 6.5%), and TLR (7.3% vs. 8.3%, $p = 0.86$) were similar between groups. These findings remained consistent after propensity score matching, suggesting that DCB angioplasty may have a role in treating selected LMS disease.

Recently, a sub-analysis of the large prospective multicenter EASTBOURNE registry (NCT03085823) [31, 32] analyzed the safety and efficacy of Magic Touch (Concept Medical, USA) sirolimus-coated balloons in a cohort of patients with large coronary arteries (>2.75 mm as RVD). Clinically-driven TLR at 2 years in the 757 patients/810 lesions enrolled (mean RVD was 3.2 ± 0.3 mm, lesion length 22 ± 7 mm) occurred in 9% of the patients, with 4% of MI and 4.5% of all-cause deaths. ISR ($n = 629$) and de novo ($n = 181$) lesions were associated with 11% and 4% rates of TLR at 2 years, respectively [33].

Although several observational studies suggest that DCB may be an alternative for de novo lesions in large vessels, clear evidence of their long-term efficacy and safety is limited. Large, adequately powered randomized trials with long-term follow-up are required to determine their role compared with contemporary DES. One such completed pivotal study is REC-CAGEFREE I, which will be discussed in detail in the next section. On-going studies include the REVERSE trial (NCT05846893), a multicenter, randomized study of de novo large vessel disease (≥3.0 mm), enrolling 1436 patients to compare the SeQuent Please NEO PCB with current-generation DES. The primary endpoint is 1-year net adverse clinical events (NACE), with follow-up planned through 3 years. The BOOST-AMI trial (NCT06746233) is another ongoing multicenter study, enrolling patients with STEMI who have de novo culprit lesions that have been successfully prepared, in vessels with an RVD between 2.5 and 4.0 mm. A total of 598 patients are planned for enrollment and will be randomized to either PCB or second-generation DES. The primary endpoint is the 1-year DoCE, with follow-up extending to 2 years.

20.10 Randomized Trial for De Novo All-Size Vessel—REC-CAGEFREE I: 3-Year Results

The REC-CAGEFREE I trial (NCT04561739) represents the first large-scale randomized investigation to provide 3-year follow-up data comparing DCB angioplasty with DES for de novo coronary artery disease, irrespective of vessel size [24]. Conducted across 43 centers in China, this open-label, non-inferiority trial enrolled 2272 patients with non-complex de novo lesions following successful predilatation. Participants were randomized 1:1 to PCB angioplasty with optional rescue stenting (Swide, Shenqi Medical, Shanghai, China; DCB arm, n = 1133) or to planned implantation of second-generation thin-strut sirolimus-eluting stents (Firebird 2, MicroPort, Shanghai, China; DES arm, n = 1139). The median device diameter was 3.0 ± 0.46 mm, reflecting a predominantly large-vessel population.

At 3-year follow-up, DoCE, a composite of cardiovascular death, TV-MI, and clinically and physiologically indicated TLR (CPI-TLR), occurred in 8.2% of patients in the DCB arm vs. 5.0% in the DES arm (difference 3.21%, 95% CI 1.17–5.26; HR 1.68 [1.21–2.34]; p = 0.002). Individually, cardiovascular death occurred in 3.0% vs. 2.5% (p = 0.43), TV-MI in 2.0% vs. 1.8% (p = 0.63), and CPI-TLR in 4.2% vs. 1.6% (p < 0.001) in the DCB and DES groups, respectively.

Landmark analysis showed that the between-group differences in DoCE were largest in the first year (1.69%, p = 0.016), and progressively decreased during the second (1.10%, p = 0.079) and third year (0.58%, p = 0.30), indicating no excess late hazard with DCB therapy. There were no significant treatment-by-subgroup interactions for the primary endpoint in numerous prespecified subgroup analyses. However, compared with the small-vessel (RVD <3.0 mm) subgroup, patients with non–small vessel disease (RVD ≥3.0 mm) tended to have a higher risk of DoCE when treated with DCB angioplasty (HR 1.21, 95% CI 0.75–1.97 vs. HR 2.22, 95% CI 1.40–3.51, $P_{\text{interaction}}$ = 0.078). Rescue stenting was required in 9.4% of patients treated with DCB, and these patients showed a trend toward a higher rate of DoCE at 3 years compared with those who did not require rescue stenting (10.4% vs. 7.9%). At 3 years, major bleeding events (Bleeding Academic Research Consortium [BARC] type 3 or 5) were numerically less frequent in the DCB group (1.4% vs. 2.6%). At 6 and 12 months, de-escalation of DAPT was more frequent in the DCB group, with a higher proportion of patients switching to single antiplatelet therapy earlier than in the DES arm.

Although non-inferiority to DES was not achieved, this study provides crucial evidence that a metal-free DCB strategy remains safe and clinically stable over time, with rates of death and MI comparable to DES. The findings underscore the importance of meticulous lesion preparation and careful patient and lesion selection, particularly in large vessels, to minimize early recoil and the need for bailout stenting [24, 34].

20.11 Interpretation of Available Data

Evidence from both randomized trials and real-world studies demonstrates that DCB therapy provides long-term efficacy and safety comparable to DES in ISR and de novo small vessel lesions. Importantly, whilst the 3-year results of REC-CAGEFREE I showed that DCB angioplasty was associated with a higher rate of DoCE compared to DES implantation, especially in large vessels, the between-group differences gradually decreased with longer follow-up. The study will continue to report on these differences with follow-up planned out to 10 years. The SELUTION DeNovo trial (NCT04859985) [35] is an ongoing multicenter study that enrolled 3323 patients with de novo lesions across all vessel sizes (2–5 mm), who were randomized to a novel sirolimus-eluting balloon (Selution SLR DEB, Cordis) or contemporary DES. At 1 year, the Selution DEB met non-inferiority for the primary endpoint of TVF compared with DES (5.3% vs. 4.4%, P for non-inferiority = 0.02). Follow-up will continue for 5 years and is

expected to provide important insights into long-term outcomes [36].

Among the available studies, angiographic follow-up after DCB treatment has only been limited to 1 year. From a safety perspective, performing invasive angiographic follow-up over a longer period may not be ideal due to the risk of rare but serious complications and medical costs. On the other hand, non-invasive coronary CT angiography (CCTA) may have a potential role in the long-term follow-up of patients after PCI with DCB, as the coronary artery is free of a metallic implant, which can cause blooming artifacts. CCTA enables evaluation not only of anatomical surrogate endpoints such as minimum lumen area (MLA), plaque burden (PB), and vessel remodeling, but also of plaque composition and vulnerability. In addition, FFR-CT allows physiological assessment of treated lesions, which may help elucidate the long-term consequences of acute procedural results. With the introduction of photon-counting CT, image quality has markedly improved, potentially enabling more detailed and accurate assessments and generating new insights into long-term vessel healing.

Another important aspect for potentially improving long-term outcomes is the use of optimal medical therapy (OMT) for secondary prevention. The current guidelines give a Class I recommendation for lipid-lowering therapy with an LDL-C goal of <1.4 mmol/L (55 mg/dL) [14]. The use of high-intensity statins up to the highest tolerated dose is recommended, with ezetimibe and PCSK9 inhibitors considered if the LDL-C target is not reached. The long-term impact of OMT on DCB-treated lesions has not yet been examined. CCTA may facilitate the assessment of the potential synergistic effects of DCB and intensive OMT on plaque composition and regression, which could become an emerging focus for long-term follow-up studies.

In complex lesions such as bifurcation lesions and diffuse lesions, longer and multiple stents are often required, increasing the risk of stent thrombosis, ISR, prolonged DAPT, and consequently major bleeding, all of which may lead to worse outcomes. Combination therapy using both DES and DCB may offer prognostic benefits in these settings. The DCB-BIF study evaluated patients with bifurcation lesions in which DES were implanted in the main vessel, and either a DCB or a non-compliant balloon (NCB) was used for the side branch [37, 38]. At 1-year follow-up, the DCB group had a lower rate of MACE than the NCB group. In addition, registry data have also shown the long-term efficacy and safety of combination therapy with DCB and DES in diffuse lesions, chronic total occlusions, left main bifurcations, and multivessel disease [38–47]. Moreover, novel scaffold technologies may further enhance the long-term outcomes of combination therapy. DynamX Bioadaptor stent (Elixir Medical Corporation, USA) is designed to "uncage" after resorption of the bioresorbable polymer coatings over six months, allowing vessel motion and adaptive remodeling while maintaining vessel lumen [48, 49]. After uncaging, the device continues to provide dynamic support to the diseased vessel and enables restoration of hemodynamic modulation of the artery. Bioresorbable scaffold (BRS) technology is also being improved. When combined with DCB therapy, a BRS may help achieve a true "leave-nothing-behind," metal-free PCI strategy. The development of new-generation BRS, alongside ongoing innovations in DCB therapy, may help advance metal-free PCI.

20.12 Conclusion

Long-term follow-up results from randomized controlled trials have shown that DCB provide efficacy and safety comparable to contemporary DES in treating ISR and de novo small-vessel disease. Long-term data on DCB use in de novo large-vessel disease remain limited, but large ongoing randomized trials are expected to provide further insights into their role. In real-world practice, PCI is often performed for complex lesions such as bifurcations, diffuse lesions, chronic total occlusions, and multivessel disease, where DES-only strategies may be associated with less favorable clinical outcomes, and a combination approach incorporating DCB

therapy may offer advantages. Advances in device technology (DCB, lesion-preparation devices, scaffolds), optimization of intracoronary imaging, and appropriate OMT, including antithrombotic and lipid-lowering therapy, are likely to improve the long-term outcomes of DCB-based PCI.

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The Role of Drug-Coated Balloons for the Treatment of Peripheral ISR

21

Irfan Ullah, Julia Tirelli, Nicholas Pennza, Shamin Hayat Mahmud, and Bernardo Cortese

21.1 Introduction

Peripheral arterial disease (PAD) affects multiple vascular territories including the iliac, femoropopliteal, infrapopliteal, renal, mesenteric, subclavian, and carotid arteries, affecting more than 200 million individuals worldwide and is strongly associated with functional decline, limb-threatening ischemia and major cardiovascular morbidity and mortality [1]. Over the past two decades, endovascular therapy has become the first-line approach for most femoropopliteal and iliac lesions due to lower morbidity, faster recovery and limb-related outcomes comparable to bypass surgery [2, 3]. Stent implantation remains fundamental in modern practice by providing immediate luminal gain, stabilizing dissections, and preventing recoil—especially in complex lesions or mechanically stressed segments. Both bare-metal stents (BMS) and nitinol drug-eluting stents (DES) continue to play central roles, supported by randomized evidence such as the RESILIENT trial [4].

However, despite advances in device technology and procedural technique, in-stent restenosis (ISR) has emerged as one of the most challenging limitations of peripheral interventions. ISR reflects a complex biological and mechanical process dominated by neointimal hyperplasia and chronic inflammation, and recurrence after repeat angioplasty is common [5, 6]. Iliac ISR may cause recurrent claudication or pelvic ischemia; femoropopliteal ISR is particularly common due to the extreme mechanical forces acting on the superficial femoral and popliteal arteries; infrapopliteal ISR can jeopardize limb salvage in patients with critical limb-threatening ischemia, each with its own anatomic constraints and technical considerations [7, 8]. Across all territories, ISR represents a failure of vessel healing characterized by neointimal hyperplasia, chronic vessel injury, stent fatigue and sometimes extrinsic compression or repetitive motion.

Traditionally, plain balloon angioplasty (POBA) has been considered the gold-standard approach for the treatment of peripheral ISR because it is widely available, easy to perform and avoids placing an additional stent layer. Nevertheless, POBA is limited by poor long-term patency, high rates of recurrent restenosis, and

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frequent need for repeat target lesion revascularization particularly in femoropopliteal ISR, findings consistently demonstrated across observational studies and comparative trials [5, 9, 10] Repeat stenting, although effective acutely, increases metal burden, reduces vessel compliance, and may compromise future revascularization options. Moreover, repeat stenting is associated with a high risk of recurrences.

Modern advances in endovascular stent design have overcome many of the shortcomings of conventional percutaneous transluminal balloon angioplasty in lower-extremity PAD, including elastic recoil, incomplete lesion expansion, and flow-limiting dissections [11–13]. Despite these improvements, in-stent restenosis remains a frequent cause of treatment failure, and a substantial number of stented patients ultimately require repeat revascularization, particularly when lesions are long, diffuse, or anatomically complex [14, 15].

Within this therapeutic gap, drug-coated balloons (DCBs) have emerged as a promising and increasingly utilized modality for the management of peripheral ISR. By delivering an antiproliferative drug to the arterial wall without leaving a permanent implant, DCBs directly target the biological mechanisms driving restenosis while preserving the vessel's natural compliance and avoiding the drawbacks of repeat stenting. Randomized and multicenter studies, including FAIR, PACUBA, and global real-world cohorts have shown that DCB significantly improve patency and reduce target lesion revascularization (TLR) compared with POBA in femoropopliteal ISR [9–18].

As the prevalence of peripheral interventions continues to rise, and with it the incidence of ISR, understanding the role of DCB across different vascular territories has become essential. This chapter reviews the mechanisms of peripheral ISR, the evolving evidence base supporting DCB therapy, and practical considerations for optimizing outcomes in patients with stent failure throughout the peripheral vasculature.

21.2 Classification of Peripheral In-Stent Restenosis

Peripheral ISR can be categorized according to its morphologic (angiographic) characterstics. ISR has been reported to occur in approximately 18–40% of patients undergoing femoropopliteal stenting within the first year after of treatment [19, 20]. Tosaka et al. proposed a classification system for femoropopliteal ISR [5], in which ISR lesions are assigned in one of three categories based on angiographic features additional frameworks have become increasingly relevant in the current era, particularly when evaluating treatment strategies such as DCB angioplasty vs. POBA (Fig. 21.1).

21.2.1 Morphological Classification (Tosaka)

Class I: Focal ISR

- Lesion length ≤50 mm.
- Often at edges or stent body.

Class II: Diffuse ISR

- Lesion length >50 mm.
- Stent body and edges [21, 22].

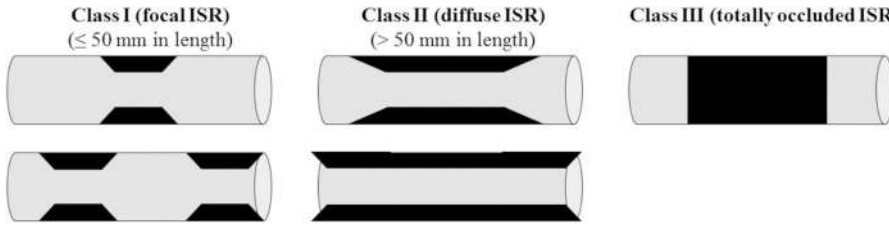


Fig. 21.1 Tosaka femoropopliteal ISR classification. (Reproduced from Ref. [5], with permission)

Class III: Occlusive ISR

- Complete stent occlusion.
- Within the entire length of stent.

At two years of follow-up, patients with Class III ISR experience the highest rates of failure, with recurrent restenosis observed in 84.8% of cases, compared with 49.9% in Class I and 53.3% in Class II lesions ($p < 0.0001$ and $p = 0.0003$, respectively). Likewise, reocclusion occurs far more frequently in Class III ISR, affecting 64.6% of patients, whereas substantially lower rates were seen in Class I (15.9%) and Class II (18.9%) groups (both $p < 0.0001$) [5]. Both the angiographic pattern of restenosis and the reference vessel diameter following femoropopliteal stent implantation independently influence the risk of subsequent restenosis and reocclusion. Although balloon angioplasty for stenotic ISR is feasible, freedom from recurrent ISR and occlusion after balloon angioplasty is remarkably low for totally occluded ISR [5].

In a separate cohort of 75 femoropopliteal ISR cases, Class III ISR was associated with significantly worse outcomes, with recurrent restenosis occurring in 72% of patients at 2 years, compared with 39% in Class I and 67% in Class II lesions ($P = 0.04$). Similarly, total stent occlusion rates were 52% in Class III, vs. 8% in Class I and 11% in Class II ($P = 0.009$). Class III ISR was independently associated with recurrent ISR (HR 2.4; 95% CI 1.1–5.6) and recurrent occlusion (HR 5.8; 95% CI 1.8–19.0), reinforcing the prognostic importance of lesion morphology and supporting more aggressive treatment strategies for occlusive ISR [23].

21.3 Endovascular Treatment of Peripheral In-Stent Restenosis

Peripheral arterial ISR continues to pose major challenges across vascular beds because of mechanical forces, neointimal hyperplasia, elastic recoil and chronic inflammatory responses within the stent frame. Given the high likelihood of recurrent stenosis, contemporary endovascular management prioritizes thorough vessel preparation, optimized luminal gain and durable antiproliferative suppression while minimizing the addition of new metal layers whenever possible.

Since the previous edition, a growing body of data across all peripheral territories has clarified the roles of POBA, high-pressure and specialty balloons, atherectomy, laser debulking, DES and covered stents in treating ISR. Across studies, POBA consistently demonstrates the lowest effect durability, especially in the femoropopliteal system, where only 30–40% of luminal patency is typically maintained at 12 months [5, 9]. Cutting balloons have shown improved midterm patency compared with conventional angioplasty [24], while scoring balloons reduce bailout stenting rates relative to high-pressure balloons [25]. Atherectomy has also demonstrated some benefits in select lesions with high plaque burden: Armstrong et al. reported that laser atherectomy followed by POBA significantly lowers TLR compared with POBA alone [26], and Milnerowicz et al. showed that rotational atherectomy improves technical success in occlusive ISR with consistent outcomes [27].

Covered stents remain a strong option when recoil or dissection are present. The VIASTAR-ISR analysis demonstrated superior luminal preservation with covered stents compared with plain balloons [28]. In contrast, DES re-stenting shows more modest durability, with Zilver PTX registry updates reporting primary patency of 45–55% in the same follow-up period for ISR lesions [29].

In the iliac system where ISR is relatively uncommon and restenosis risk is lower, covered stents generally provide the most favorable outcomes, consistently outperforming both plain balloon angioplasty and bare-metal stents, with luminal preservation of approximately 80–85% at one year [30, 31]. A multinational registry also demonstrated significantly lower TLR with covered stents compared with BMS at 1–2 years [30]. In contrast, simple angioplasty remains associated with higher recurrence and is not usually performed in this district [30, 31].

Lastly, other peripheral sites deserve to be mentioned. Renal ISR, now uncommon, typically responds well to repeat stenting; covered stents

are reserved for cases of recoil or rupture [7, 32]. Mesenteric ISR is rare and data are limited, though outcomes generally parallel those of other visceral vessels, with covered stents offering the most durable results [33, 34].

21.4 Drug-Coated Balloons in Peripheral In-Stent Restenosis

The femoropopliteal (FP) segment represents the vascular bed with the strongest and most consistent evidence supporting DCB use in ISR. Multiple randomized controlled trials have shown significant improvements in both angiographic and clinical outcomes compared with POBA, as shown in Table 21.1 [9, 10, 35–37].

An illustrative case of femorpopliteal superficial femoral artery (SFA) ISR treated with laser atherectomy and IN.PACT drug-balloon (5 × 150 mm), showing excellent final angiographic results (Fig. 21.2).

Early randomized studies such as the PACUBA trial demonstrated a 12-month primary patency of 40.7% with DCB vs. 13.4% with POBA [10]. The FAIR trial further confirmed these findings, reporting significantly lower recurrent restenosis and TLR rates at both 6 and 12 months in the DCB arm compared with POBA [9]. Longer-term follow-up by the ISAR-PEBIS trial, in which TLR at 24 months occurred in 19% of DCB-treated patients compared with 50% in the POBA group, shows a relative reduction of this type of events of more than 60% [17]. Similarly, the COPA-CABANA trial showed significantly reduced late lumen loss at 6 months and lower TLR at 2 years following DCB treatment compared with uncoated balloons [18].

The DEBATE-ISR trial, conducted in diabetic patients, highlighted the influence of long-term follow-up and patient risk profile [39, 40]. While restenosis at 12 months was significantly lower with DCB (13.6% vs. 31.0%), the benefit diminished over time, with 3-year TLR rates of 40% in the DCB group vs. 43% with POBA ($p = 0.8$), suggesting attenuation of benefit over time in high-risk cohorts.

More contemporary randomized data from LIAO et al. confirmed these benefits, reporting 12-month primary patency of 87.9% in the DCB group vs. 51.6% with PTA, alongside a marked reduction in TLR (6.1% vs. 35.5%) [16]. These results represent one of the largest absolute differences favoring DCB in FP-ISR.

Observational and single-arm studies support these randomized findings. The PLAISIR trial ($n = 53$) reported freedom from TLR of 90.2% at 12 months [41], while Stabile et al. observed a 12-month primary patency of 92.1% with DCB plus PTA [42]. The IN.PACT Global ISR Imaging Cohort ($n = 131$) similarly demonstrated high patency and low TLR at 12 months, reinforcing real-world applicability [43].

Long-term durability was addressed by Horie et al. using propensity score matching. At 5 years, paclitaxel-coated balloon angioplasty achieved primary patency of 65.7% vs. 18.7% with PTA alone, and freedom from TLR of 77.6% vs. 53.8%, underscoring sustained benefit in FP-ISR [44].

Collectively, these data indicate that DCB consistently improve primary patency by 25–40% and reduce TLR by approximately 50–70% compared with uncoated balloons, in FP-ISR, particularly within the first 12–24 months, all the details given in Table 21.1 [9, 10, 16–18, 39–45].

In iliac ISR, DCB have been explored mainly in small, single-center studies. Limited single-center series suggest that DCB angioplasty may be effective for focal iliac ISR, although evidence remains sparse and outcomes are generally favorable regardless of treatment strategy [46]. Beyond the femoropopliteal and iliac segments, evidence for DCB use in other peripheral ISR locations remains limited. In infrapopliteal ISR, most studies show no clear advantage of paclitaxel-based angioplasty over plain balloon strategy [47, 48]. Data regarding renal artery in-stent restenosis remain sparse and are largely limited to small retrospective series; repeat stenting remains the most commonly adopted strategy [7, 32]. Similarly, data on DCB use in mesenteric ISR remain extremely limited, and covered stents continue to be the preferred treatment strategy [33, 34].

Table 21.1 Studies on DCB use for the treatment of peripheral ISR

Study name/Author	Country/Region	Study Design	Comparison	Population and lesion	Sample size/ Follow up	Main findings
PACUBA (Kinstner et al. 2016) [10]	Germany	Randomized controlled trial	Paclitaxel DCB vs. POBA	Femoropopliteal ISR	74 patients 12 months	Primary patency 40.7% in DCB group vs. 13.4% in PTA one at 12 months
Liao et al. (2019) [16]	China	Randomized controlled trial	Paclitaxel DCB vs. POBA	Femoropopliteal artery ISR	74 patients 12 months	DCB show higher primary patency (87.9% vs. 51.6%) & lower TLR (6.1% vs. 35.5%) vs. PTA group at 12 months
ISAR-PEBIS (Ott et al. 2017) [17]	Germany	Randomized controlled trial	Paclitaxel DCB vs. POBA	Superficial Femoral Artery ISR	70 patients 24 months	DCB are associated with less TLR in compare to BA (19% vs. 50%) at 24 months
FAIR (Krankenberg et al. 2015) [9]	Multicenter (Germany)	Randomized controlled trial	Paclitaxel DCB vs. POBA	Superficial Femoral Artery ISR	119 patients 12 months	DCB show lower recurrent restenosis and TLR at 6 and 12 months compared to POBA
COPA CABANA (Tepe et al. 2020) [18]	Multicenter (Germany & Switzerland)	Randomized controlled trial	Paclitaxel DCB vs. POBA	Superficial Femoral Artery & popliteal ISR	88 patients 24 months	DCB significantly reduce late lumen loss at 6 months and TLR at 2 years compared to uncoated balloon
DEBATE-ISR (Liistro et al. 2014; Grotti et al. 2016) [39, 40]	Italy	Randomized controlled trial	Paclitaxel DCB vs. POBA	Femoropopliteal ISR (in diabetic patients)	44 patients 12–36 months	DCB reduce restenosis by 13.6% compared to BA by 31.0% at 12 months But TLR at 3 years was 40% in the DCB vs. 43% in the BA group ($p = 0.8$)
PLAISIR Trial (Bague et al.) [41]	France	Single arm trial	Paclitaxel DCB	Femoropopliteal ISR	53 patients 18 months	DCB show freedom from TLR was 90.2% at 12 months
Stabile et al. (2012) [42]	Italy	Prospective registry	Paclitaxel DCB	Superficial Femoral Artery ISR	39 patients 12 months	DCB show higher primary patency rate (92.1%) at 12 months
Horie et al. (2021) [44]	Japan	Propensity score matching	Paclitaxel DCB vs. POBA	Femoropopliteal ISR	50 patients 5 years	PCB shows significantly higher patency (65.7% vs. 18.7%) and freedom from TLR (77.6% vs. 53.8%) compared to without PCB
IN.PACT Global ISR Imaging Cohort (Brodmann et al. 2017) [43]	Multinational	Prospective single-arm registry	Paclitaxel DCB	Femoropopliteal ISR	131 patients 12 months	DCB show high patency and a low TLR at 12 months
Zhang et al. (2021) [45]	China	Retrospective	DCB	Femoropopliteal ISR	28 patients 14 months	DCB is safe and effective in treating femoropopliteal ISR lesions (Tosaka class III)

DCB drug-coated balloon, *ISR* in-stent restenosis, *PCB* paclitaxel-coated balloon, *TLR* target lesion revacularization

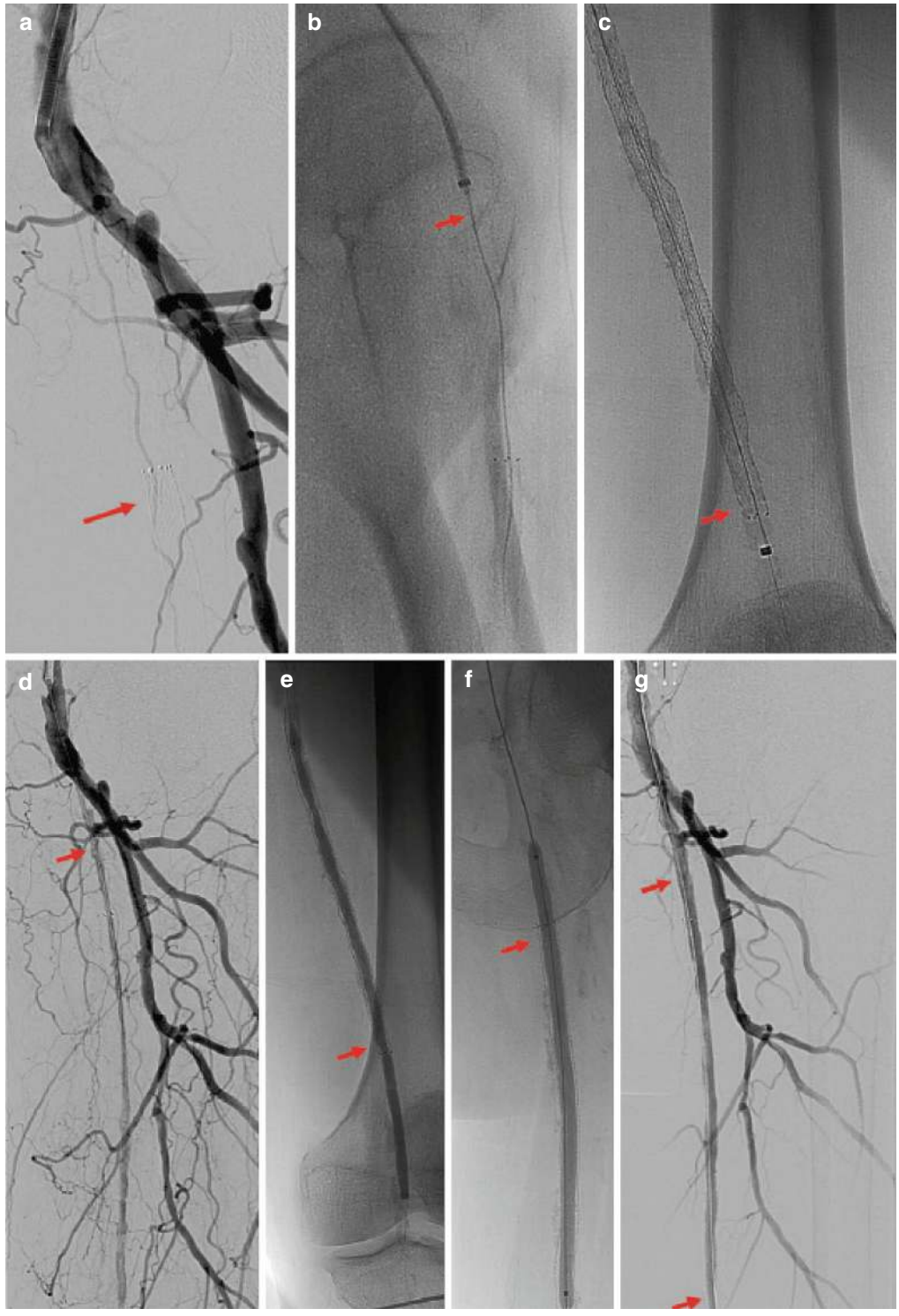


Fig. 21.2 A case of SFA ISR treated with laser atherectomy and DCB. Legend: (**a**) Baseline angiography, (**b**, **c**). Lesion access and laser atherectomy (2.3-mm Turbo-Power catheter) within the occluded stent, (**d**). Angiography after laser atherectomy, (**e**). Vessel preparation with a 5-mm scoring balloon, (**f**). IN.PACT DCB (5 × 150 mm) were used. (**g**) Final angiography demonstrating excellent results and no significant dissection. (Reproduced with permission from Ref. [38])

21.5 Debulking Followed by DCB for the Treatment of Peripheral ISR

Debulking as improved vessel preparation tool has emerged as a key determinant of DCB performance in ISR. In the setting of peripheral ISR, debulking is used to optimize luminal gain, reduce elastic recoil and improve drug penetration during subsequent DCB inflation.

Since the previous edition of this DCB Book, growing evidence has supported this combined strategy, particularly in the femoropopliteal segment. Multiple contemporary studies demonstrate that atherectomy prior to DCB therapy can enhance procedural success and may improve longer-term durability in selected ISR lesions. Observational studies and retrospective analyses suggest that debulking prior to DCB angioplasty may improve procedural success and mid-term durability in diffuse or occlusive femoropopliteal ISR, particularly in Tosaka II and III lesions [14–16].

Directional atherectomy removes plaque by excising tissue along the longitudinal axis of the vessel using a cutting mechanism, whereas *rotational atherectomy* employs a high-speed rotating burr to ablate plaque from the vessel wall, with particulate debris carried distally and subsequently cleared by phagocytosis. *Orbital atherectomy*, in contrast, utilizes an eccentrically rotating, diamond-coated crown to achieve circumferential plaque modification within the vessel lumen [49–51].

Directional atherectomy has been evaluated as a debulking strategy prior to DCB. In a retrospective study of 89 femoropopliteal ISR patients, Sixt et al. reported that directional atherectomy combined with DCB resulted in freedom from restenosis in 84.7% of the patients at 12 months, compared with 43.8% of patients treated with directional atherectomy plus POBA. A multivariable analysis showed an hazard ratio for restenosis after DCB treatment compared to PTA of 0.28 (0.12–0.66; $P = 0.0036$) [52].

Mechanical and rotational atherectomy strategies have similarly shown encouraging results. The PERMIT-ISR trial, a single-arm study including 59 patients with femoropopliteal ISR, evaluated percutaneous mechanical atherectomy with thrombectomy followed by DCB angioplasty. At 12 months, freedom from TLR was 84.7%, with primary patency of 82.5% and secondary patency of 92.5%, indicating favorable mid-term durability in a complex ISR population [53].

Milnerowicz et al. evaluated 73 patients with iliac and infrainguinal ISR treated with rotational atherectomy followed by DCB angioplasty. At 12 months, TLR was only 5.5%, supporting the feasibility of this approach beyond the femoropopliteal segment. Importantly, this study identified predictors of recurrent restenosis, which was more frequent in patients with Rutherford category 5 ischemia ($p = 0.005$), emergency procedures ($p = 0.021$), extensive interventions involving three vessel segments ($p = 0.016$), and procedural complications ($p < 0.001$), underscoring the influence of clinical severity and procedural complexity on outcomes [27]. More recent data from Wang et al. further support the safety and effectiveness of rotational atherectomy prior to DCB in femoropopliteal ISR. In 38 patients, 12-month primary patency was 86.7%, with a TLR rate of 7.9%, aligning closely with outcomes reported for laser-based strategies [54].

Finally, Li et al. directly compared DCB angioplasty alone with DCB combined with debulking (laser or rotational atherectomy) in 80 femoropopliteal ISR patients. At 12 months, primary patency was significantly higher in the debulking + DCB group (87.2% vs. 65.9%, $p = 0.039$). No significant difference was observed between laser- and rotational atherectomy–based debulking (86.4% vs. 88.2%, $p = 0.842$), suggesting that the benefit was related to plaque removal itself rather than the specific debulking modality [55].

There has only been one prospective study of this debulking modality for infrainguinal ISR. In a multicenter nonrandomized study of 33 patients, primary patency at 2 years was 25%, respectively [56]. However, the combination of directional atherectomy with DCB angioplasty offers the advantage of lesion debulking and the antirestenotic effect of DCB.

Collectively, these studies demonstrate that debulking prior to DCB angioplasty consistently improves procedural success and mid-term durability in peripheral ISR, particularly in diffuse, occlusive, or recurrent femoropopliteal ISR (Tosaka II–III). Across studies, TLR rates are typically reduced to below 10–20% at 12 months, and primary patency frequently exceeds 80% when debulking is employed. While randomized data remain limited, the concordant findings across multiple cohorts support a debulking-first strategy in selected ISR lesions to maximize the therapeutic benefit of DCB angioplasty.

Excimer laser atherectomy ablates neointimal tissue through photoablation, allowing effective debulking while minimizing injury to surrounding structures and reducing platelet activation [57, 58]. However, its use is limited by modest acute luminal gain when employed as a standalone therapy, reduced effectiveness in heavily calcified lesions, and the high cost of the technology [22]. The role of excimer laser atherectomy in the treatment of femoropopliteal in-stent restenosis has been evaluated in multiple clinical studies, as shown in Table 21.2.

In terms of DCB strategy, Gandini et al. compared excimer laser atherectomy followed by DCB with DCB alone in 48 patients with superficial femoral artery ISR. At 12 months, TLR was markedly reduced in the laser + DCB group (16.7%) compared with DCB alone (50%), indicating a three-fold relative reduction in repeat revascularization when debulking preceded drug delivery [59].

In another study by Kokkinidis et al. involving 112 patients with femoropopliteal ISR, laser atherectomy followed by DCB was associated with significantly improved outcomes compared with laser plus balloon angioplasty alone. At 12–24 months, freedom from TLR was 72.5% with laser + DCB vs. 50.5% with laser + BA ($p = 0.043$), while freedom from reocclusion was 86.7% vs. 56.9%, respectively ($p = 0.003$), highlighting both improved durability and vessel patency with the addition of DCB [60, 61].

In contrast, the Photoablative Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis in Instent Femoro-popliteal Obstructions (PHOTOPAC) randomized trial evaluated safety and efficacy of laser atherectomy before DCB angioplasty vs. plain balloon angioplasty (POBA) before DCB angioplasty, showed two-year freedom from TLR and primary patency was 63.6% vs. 72% and 56.5% vs. 53.8%, respectively [62].

Whereas, the EXCITE ISR trial randomized 250 patients to laser atherectomy with PTA vs. PTA alone for the FP ISR. Mean lesion length was 19.6 ± 12.0 mm with total occlusions in 30.5% and 36.8% of patients in the laser plus PTA and PTA groups, respectively. Six-month freedom from TLR was 73.5% in laser group vs. 51.8% in PTA ($P < 0.005$), and 30-day major adverse event rates were 5.8% vs. 20.5% ($P < 0.001$), respectively [63]. This shows that laser atherectomy help if combind with PTA compared to PTA alone. The findings from studies comparing DCB showed good results compared to PTA, showing the feasibility of debulking for lesion preparation, in selected lesion types.

Although sample sizes remain modest and data are primarily observational, these studies consistently show that vessel preparation with debulking can enhance the biological effectiveness of DCB therapy, especially in diffuse or occlusive ISR where neointimal burden limits drug penetration, probably also by allowing a more effective drug penetration into the vessel wall. As a result, many operators selectively incorporate atherectomy prior to DCB inflation in long, recurrent, or Type II/III ISR patterns [64].

21.6 Conclusion

DCB have become a cornerstone therapy for the treatment of peripheral in-stent restenosis, consistently demonstrating advantages over plain balloon angioplasty in reducing recurrent restenosis and target lesion revascularization. In the last few years, accumulating evidence has reinforced the efficacy of DCB for any type of femoropopliteal disease and has broadened the insights into the importance of achieving a correct lesion preparation, especially in the more complex

Table 21.2 Studies showing debulking before DCB for treatment of peripheral ISR

Study name/ Author	Country/study design	Comparison	Population and lesion	Sample size/ follow up	Main findings
Gandini et al. (2013) [59]	Italy RCT	Laser plus DCB vs. DCB alone	Superficial Femoral Artery ISR	48 patients 12 months	TLR at 12 months is reduced in DCB plus laser group compared to DCB only (16.7% vs. 50%)
Kokkinidis et al. (2017) [60, 61]	USA Retrospective	Laser plus DCB vs. Laser plus BA	Femoropopliteal ISR	112 patients 12–24 months	Laser plus DCB is associated with more freedom from TLR (72.5% vs. 50.5%, $p = 0.043$) and freedom from reocclusion (86.7% vs. 56.9%, $p = 0.003$) compared to laser plus BA
PERMIT-ISR Trial (Liu et al. 2021) [53]	China Single-arm trial	Percutaneous mechanical atherectomy plus thrombectomy (MATH) plus DCB	Femoropopliteal artery ISR	59 patients 12 months	In MATH with DCB group, freedom from TLR is 84.7% at 1 year. Primary patency and secondary patency rate are 82.5% and 92.5%
Wang et al. (2024) [54]	China Retrospective	RA plus DCB	Femoropopliteal artery ISR	38 patients 12 months	RA plus DCB seems safe and provides acceptable 12-month primary patency (86.7%) and TLR rates (7.9%) in femoropopliteal ISR
Milnerowicz et al. (2019) [27]	Poland Retrospective	RA plus DCB	Iliac and/or Infrainguinal Arteries ISR	73 patients 12 months	RA plus DCB angioplasty produce satisfactory outcomes in iliac and infrainguinal arteries ISR patients, TLR 5.5%
Sixt et al. (2013) [52]	Germany Retrospective	DA plus DCB vs. DA plus PTA	Femoropopliteal ISR	89 patients 12 months	The combined DA with DCB shows more freedom from restenosis compared to PTA with DA groups (84.7% vs. 43.8%)
Li et al. (2023) [55]	China Retrospective	DCB plus debulking devices (LA and RA) vs. DCB alone	Femoropopliteal ISR	80 patients 12 months	Patency is higher in debulking + DCB group (87.2% vs. 65.9%, $p = 0.039$), whereas no difference is observed in subgroup analysis between LA plus DCB vs. RA plus DCB (86.4% vs. 88.2%, $p = 0.842$)

DCB drug-coated balloon, *ISR* in-stent restenosis, *SFA* superficial femoral artery, *TLR* target lesion revascularization, *DA* directional atherectomy, *RA* rotational atherectomy, *LA* laser atherectomy

lesions settings. Although clinical outcomes remain heterogeneous and are strongly influenced by lesion morphology, vessel diameter, and the adequacy of lesion preparation, DCB continue to represent a durable, metal-free therapeutic option that preserves future treatment flexibility and avoids additional stent layering.

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22 The Role of Drug–Coated Balloon for the Treatment of Native Superficial Femoral Artery

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22.1 Evolution of Paclitaxel Drug-Coated Balloons for Superficial Femoral Artery Intervention

The superficial femoral artery (SFA) presents a particularly challenging environment for endovascular intervention due to its complex biomechanical milieu. Its long, mobile course, coupled with frequent external compression and torsional forces, predisposes treated segments to stent fracture, vessel recoil, and recurrent restenosis [1]. These mechanical stresses are further compounded by anatomic factors such as high flexion points at the adductor canal, small-caliber vessels, long diffuse lesions, and bifurcation involvement, all of which limit the durability of traditional angioplasty and stenting strategies [2, 3]. Collectively, these challenges drove the development of DCB technologies designed to achieve durable patency without the drawbacks of permanent scaffolds.

Early foundational work by Bruno Scheller and colleagues established the mechanistic rationale for using paclitaxel, an antineoplastic agent that induces mitotic arrest through microtubule stabilization, in localized vascular therapy. The strength of paclitaxel is its potent inhibition of arterial smooth muscle proliferation following mechanical vascular injury [4]. In a porcine stent model, there was a dose-dependent reduction in neointimal formation after paclitaxel-coated balloon angioplasty, achieving up to a 34% decrease in neointimal area at doses far under the threshold for systemic toxicity [5]. Early studies also confirmed that short-duration balloon contact could deliver biologically effective concentrations of paclitaxel in vivo. In a complementary study, Scheller further explored intracoronary delivery of paclitaxel dissolved in a contrast medium. A mere three-minute exposure markedly reduced diameter stenosis (55 ± 13% to 13 ± 12%) and late lumen loss (1.94 ± 0.35 mm to 0.82 ± 0.54 mm) in a dose-dependent fashion [6]. Subsequent investigations in peripheral porcine arteries yielded similar results, confirming that short-term paclitaxel exposure delivered via percutaneous transluminal angioplasty (PTA) suppresses intimal hyperplasia [7]. Together, these studies established that paclitaxel's antiproliferative effects persist despite transient arterial exposure, validating an implant-free

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drug-delivery platform and setting the stage for the first generation of clinical DCB systems.

Early clinical feasibility of paclitaxel-coated balloon (PCB) technology in the peripheral vasculature was established by the THUNDER trial, which provided the first randomized evidence of efficacy of PCBs compared with uncoated PTA in the femoropopliteal segment [8]. At six months, mean late lumen loss was markedly lower in the PCB group (0.4 ± 1.22 mm) compared with controls (1.7 ± 1.8 mm; $p < 0.001$), and was accompanied by a reduced rate of target lesion revascularization (4% vs. 37%; $p < 0.001$). This advantage translated into a durable clinical benefit over time: at 5-year follow-up, target lesion revascularization and binary restenosis in the PCB group remained significantly lower compared to controls (21% vs. 56%, $p = 0.0005$; 15% vs. 54%, $p = 0.04$) [9]. The companion FEMPAC trial reinforced these findings, demonstrating significant reductions in late lumen loss (0.5 ± 1.1 versus 1.0 ± 1.1 mm, $p = 0.031$), fewer target lesion revascularizations (3/45 vs. 14/42 patients; $p = 0.002$), and greater improvement in Rutherford class ($p = 0.045$) among patients treated with PCB compared to controls [10].

22.2 Early Clinical Validation and Regulatory Approval

Although Europe had seen the early adoption of PCB technologies, the United States entered the field later with the development of the Lutonix 035 DCB, a Bard-Lutonix collaboration aimed at establishing a domestically engineered, polysorbate-sorbitol excipient alternative. The first clinical assessment of the low-dose Lutonix DCB was undertaken in the LEVANT I trial, a prospective, randomized study designed to evaluate safety and preliminary efficacy in femoropopliteal disease [11]. Conducted across multiple European centers, the trial compared the 2 μg/mm^2 PCB with standard PTA in de novo and restenotic lesions of the femoropopliteal segment. At six months, late lumen loss was 58% lower for the Lutonix DCB group (0.46 ± 1.13 mm) than for the control group (1.09 ± 1.07 mm, $p = 0.016$). Composite 24-month major adverse events were 39% in the DCB group, including 15 target lesion revascularizations, 1 amputation, and 4 deaths, versus 46% for the control group, with 20 target lesion revascularizations, 1 thrombosis, and 5 deaths.

The subsequent LEVANT II trial served as the pivotal study for regulatory approval of the Lutonix PCB in the United States. This multicenter, randomized trial enrolled 476 patients with symptomatic femoropopliteal occlusive disease and compared treatment with the 2 μg/mm^2 Lutonix DCB to uncoated PTA [12]. The primary efficacy endpoint was primary patency at 12 months, defined as freedom from restenosis or clinically driven target-lesion revascularization (CD-TLR). The primary safety endpoint was a composite of freedom from perioperative death and from 12-month limb-related death, amputation, or reintervention. The DCB group demonstrated superior primary patency (65.2% vs. 52.6%, $p = 0.02$) and a greater proportion of patients free from primary safety events (83.9% vs. 79.0%, $p = 0.005$ for noninferiority) compared with PTA. These results led to the 2014 FDA approval of the Lutonix 035 DCB, marking the first DCB indicated for treatment of femoropopliteal disease in the U.S.

Shortly thereafter, the IN.PACT Admiral DCB from Medtronic, employing a higher paclitaxel dose of 3.5 μg/mm^2 with a urea-based excipient, received FDA approval in January 2015 following the IN.PACT SFA pivotal trial [13–15]. In that study, the DCB group achieved higher primary patency (82.2% vs. 52.4%, $p < 0.001$) and lower CD-TLR (2.4% vs. 20.6%, $p < 0.001$) compared to PTA. These regulatory milestones established DCB angioplasty as a safe and evidence-based alternative to plain balloon angioplasty for femoropopliteal disease. Early clinical adoption was rapid [16], driven by compelling efficacy data and reinforced by professional society guidelines recognizing DCB as a first-line endovascular therapy for suitable lesions [17–20].

Second-generation DCB platforms were subsequently developed to refine drug delivery, improve coating stability, and reduce the total

paclitaxel dose. The Ranger DCB (Boston Scientific) employs a 2 μg/mm^2 paclitaxel coating with a citrate-ester excipient (TransPax formulation) engineered to optimize transfer efficiency and minimize particulate loss [21]. In the pivotal RANGER II SFA trial, which randomized 381 patients with femoropopliteal disease to Ranger DCB or standard PTA, the device achieved superior 12-month primary patency (89.8% vs. 74.0%, log-rank $p = 0.0005$) and non-inferior freedom from major adverse events (94.1% vs. 83.5%, $p = 0.0013$) [22, 23].

Long-term registry data have reinforced the durability of DCB therapy beyond the one-year horizon observed in randomized trials. The IN.PACT Global Study, a prospective, multicenter registry enrolling over 1500 patients across a wide range of lesion complexities, demonstrated sustained benefit at 5 years, with freedom from CD-TLR of 70.9% and freedom from all-cause mortality of 78.9% [24]. These outcomes were achieved in a population that included long lesions, chronic total occlusions, in-stent restenosis, and a high prevalence of diabetes—features typically underrepresented in randomized trials. Subgroup analysis confirmed consistent benefit across these challenging anatomic and clinical subsets, highlighting the robustness of DCB efficacy in routine practice [25–28]. An overview of the major randomized trials evaluating DCB platforms, including trial design and outcomes, is presented in Table 22.1.

22.3 Optimization of Paclitaxel Dose Density and Excipient Technology

Subsequent inquiry in the field challenged the assumption that higher paclitaxel dose density necessarily yielded superior long-term outcomes. The COMPARE trial, a randomized, multicenter study, directly evaluated the low-dose Ranger DCB (2 μg/mm^2) against the higher-dose IN.PACT Admiral DCB (3.5 μg/mm^2) in patients with femoropopliteal disease. At 12 months, the Ranger DCB achieved non-inferior primary patency (83.0% vs. 81.5%, p non-inferiority <0.01) and comparable freedom from major adverse events (91.0% vs. 92.6%, p non-inferiority <0.01) [29]. Extended 24-month follow-up confirmed the durability of these findings, demonstrating sustained non-inferiority despite a nearly 40% reduction in nominal paclitaxel dose [30].

Parallel evidence emerged with the SurVeil DCB (Surmodics/Abbott), which utilizes a similar low-dose (2 μg/mm^2) microcrystalline paclitaxel coating with a polyethylene-glycol-based excipient designed to enhance coating uniformity and drug transfer [31]. The TRANSCEND trial, a large randomized head-to-head comparison of SurVeil versus the higher-dose IN.PACT Admiral (3.5 μg/mm^2), demonstrated noninferiority in primary safety (91.8% vs. 89.8%, p for non-inferiority <0.001) and primary efficacy (82.2% vs. 85.9%, p for non-inferiority = 0.003) at 24 months, confirming that lower-dose formulations could achieve equivalent efficacy to established high-dose devices [32].

Complementing these randomized findings, the PROSPECT MONSTER registry in Japan provided real-world insights into dose-intensity performance among contemporary DCB [33]. This large, multicenter, pragmatic real-world analysis compared outcomes of second-generation low-dose systems (Ranger) with high-dose devices (IN.PACT) in symptomatic femoropopliteal disease. At one year, primary patency rates (87.0% vs. 81.3%, $p = 0.79$) and post-DCB impaired flow (13.6% vs. 9.8%, $p = 0.24$) were similar between groups. The consistency of these results reinforced that drug-delivery efficiency, coating stability, and excipient formulation were more deterministic of performance than nominal paclitaxel dose.

22.4 Controversies and Safety Reassessment of Paclitaxel-Coated Devices

In December 2018, Katsanos et al. published a meta-analysis in the *Journal of the American Heart Association* that fundamentally challenged prevailing assumptions on paclitaxel safety [34].

Table 22.1 Randomized and pivotal trials of DCB for femoropopliteal intervention

Trial name (Year)	Balloon type	Study arms	Primary outcome	Key findings
THUNDER (2008)	Paclitaxel DCB (early gen)	PCB vs. PTA	Late lumen loss (6 months)	Lower late lumen loss; fewer CD-TLR; 5-years durability
FEMPAC (2008)	Paclitaxel DCB (early gen)	PCB vs. PTA	Late lumen loss (6 months)	Reduced late lumen loss; fewer TLRs
LEVANT I (2014)	Lutonix 035, paclitaxel 2 μg/mm^2 (polysorbate-sorbitol)	Lutonix DCB vs. PTA	Late lumen loss (6 months)	Lower late lumen loss; similar safety at 24 months
LEVANT II (2014)	Lutonix 035, paclitaxel 2 μg/mm^2	Lutonix DCB vs. PTA	Primary patency (12 months)	Higher primary patency; non-inferior safety
IN.PACT SFA (2015)	IN.PACT admiral, paclitaxel 3.5 μg/mm^2 (urea)	IN.PACT DCB vs. PTA	Primary patency (12 months)	Higher primary patency & lower CD-TLR
ILLUMENATE Pivotal (2017)	Stellarex, paclitaxel 2 μg/mm^2 (PEG-8000 excipient)	Stellarex DCB vs. PTA	Primary patency (12 months)	Higher patency (~76% vs. 58%); favorable safety
RANGER II SFA (2021)	Ranger, paclitaxel 2 μg/mm^2 (TransPax)	Ranger DCB vs. PTA	Primary patency (12 months)	Higher primary patency; non-inferior safety
COMPARE (2020–2022)	IN.PACT 3.5 vs. Ranger 2 μg/mm^2	High-dose vs. low-dose paclitaxel DCB	Primary patency (12–24 months)	Low-dose non-inferior to high-dose at 12 and 24 months
TRANSCEND (2025)	SurVeil, paclitaxel 2 μg/mm^2 (PEG-based) vs. IN.PACT 3.5	SurVeil DCB vs. IN. PACT DCB	Primary safety/ efficacy (24 months)	Non-inferior efficacy and safety
REAL-PTX (2019)	Zilver PTX DES vs. paclitaxel DCB strategy	DES vs. DCB (± bailout stent)	Primary patency (12 months)	Similar 12-mo patency; trend favoring DES at 36 months
SIRONA (TCT 2024 interim)	Sirolimus-coated vs. paclitaxel-coated DCB	SCB vs. PCB (femoropopliteal)	Primary patency (12 months)	SCB non-inferior (73.8% vs. 75.0%); similar safety
RAPID (2019)	LEGFLOW DCB 3 μg/mm^2 + Supera vs. Supera	Supera + DCB vs. Supera	Primary patency (2 years)	No difference in 2-years patency; similar outcomes
SWEDEPAD-1 (CLTI; 2025)	Paclitaxel-coated devices	Drug-coated vs. uncoated	Major amputation; mortality	No difference in amputation/mortality
SWEDEPAD-2 (IC; 2025)	Paclitaxel-coated devices	Drug-coated vs. uncoated	Mortality (long-term)	No sustained mortality signal; similar reintervention
BASIL-3 (2025)	DCB (PCB) & DES vs. PBA ± BMS	PBA ± BMS vs. DCB ± BMS vs. DES	Amputation-free survival	Neutral across arms

Trials span early PCB vs. PBA, device/dose comparisons, and national safety-strategy programs. Outcomes are reported as in each study; key findings emphasize patency, CD-TLR, and safety

PCB paclitaxel-coated balloon, *PBA* plain balloon angioplasty, *DES* drug-eluting stent, *CD-TLR* clinically driven target lesion revascularization, *IC* intermittent claudication, *CLTI* chronic limb-threatening ischemia

Pooling data from published and unpublished randomized controlled trials (RCT), most with intermittent claudication, the authors found a 68% higher relative risk of all-cause mortality at 2 years (7.2% vs. 3.8%; RR, 1.68; 95% CI 1.15–2.47) and a 93% higher risk at 5 years (14.7% vs. 8.1%; RR, 1.93; 95% CI 1.27–2.93) among patients treated with paclitaxel-coated devices compared with uncoated controls. The signal was observed for both DCB and DESs, with a subgroup analysis showing a 44% increased risk of death for DCB alone (RR, 1.44; 95% CI 1.04–2.00). Furthermore, the authors reported a dose-response relationship, estimating a mortality risk rising 0.4% per paclitaxel milligram-year of exposure ($p < 0.001$).

Soon after, questions arose regarding the accuracy and biological plausibility of the mortality signal. A central critique was that none of the RCT included in the analysis had been designed or powered to assess all-cause mortality, as most were efficacy studies focused on restenosis and patency outcomes [35, 36]. Several additional limitations were highlighted: some included devices were early-generation systems not approved by the FDA, follow-up was often incomplete, there was crossover between study arms, and deaths were inconsistently adjudicated. Moreover, paclitaxel toxicity at the doses used in peripheral interventions was considered physiologically implausible, given that systemic exposure from DCB is minimal, yet the meta-analysis suggested mortality rates exceeding those seen with orders of magnitude higher chemotherapy doses [37, 38].

Nevertheless, the FDA responded swiftly. In January 2019, it issued its first *Letter to Health Care Providers* acknowledging the mortality signal and announcing an investigation [39]. Still, the letter emphasized "the benefits continue to outweigh the risks for approved paclitaxel-coated balloons and paclitaxel-eluting stents when used in accordance with their indications for use." Two months later, a second FDA letter adopted a more cautious tone: "For most patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents should generally be used until additional analysis of the safety signal has been performed." [40]. In Europe, clinical trials such as SWEDEPAD and BASIL-2 (more below) temporarily suspended enrollment [41].

The ensuing uncertainty triggered a rapid series of large-scale analyses reexamining mortality among patients treated with paclitaxel-coated devices. The first of these, published by Secemsky et al. in *JAMA Cardiology* in February 2019, analyzed 16,560 Medicare beneficiaries undergoing femoropopliteal revascularization and found similar 600-day mortality between patients with drug-coated (32.5%) and uncoated (34.3%) device groups; after multivariable adjustment, no association between paclitaxel exposure and death was observed [42]. A patient-level meta-analysis published in *JACC* in May 2019 pooled data from four prospective IN.PACT trials with approximately 2000 participants followed for up to 5 years, and likewise found no correlation between paclitaxel dose and mortality, with freedom from death of 85.8%, 84.2%, and 88.2% across low-, medium-, and high-dose groups, respectively [43].

Over subsequent years, progressively larger and more definitive analyses were completed. In May 2021, the SAFE-PAD study of 168,000 Medicare beneficiaries who underwent femoropopliteal revascularization reported similar 5-year mortality between paclitaxel-coated and uncoated (53.8% vs. 55.1%), confirming no excess risk across the largest cohort to be studied to date [36]. These findings were reinforced by an updated patient-level meta-analysis published in *The Lancet* in November 2023 that combined data from 2666 participants with nearly complete five-year follow-up, showing no association between paclitaxel dose and mortality [44]. Most recently, the final SAFE-PAD update reaffirmed the absence of any mortality difference between drug-coated and uncoated devices at 7-years follow-up [45]. Collectively, these studies provided the evidence base for regulatory agencies to reverse earlier warnings [46–48].

In July 2023, the FDA issued an updated *Letter to Health Care Providers*, titled "Paclitaxel-Coated Devices to Treat Peripheral Arterial Disease Unlikely to Increase Risk of Mortality," which formally restored the regulatory standing

of paclitaxel-coated technologies [49]. Current guidelines now reflect this consensus: both the 2024 SCAI/ACC/AHA and 2024 ESVS recommendations endorse paclitaxel-coated balloons and stents as safe and effective for femoropopliteal intervention when used according to approved indications, without restrictions related to prior safety concerns [50, 51].

Yet by the time the evidence had caught up, clinical confidence had not. A recent *JACC* analysis of national utilization data showed that DCB use for femoropopliteal revascularization declined by nearly one-third after 2018, reaching its lowest point in 2020, before gradually rebounding after the 2023 FDA communication [52]. Despite this rebound, utilization remains pre-controversy levels, underscoring the enduring impact of the 2018 safety debate on clinical practice. The evolution of DCB development, safety controversies, and regulatory milestones is summarized in Table 22.2.

Table 22.2 Timeline of DCB development and safety re-evaluation

Year/date	Milestone
2003	Porcine/coronary studies demonstrate local paclitaxel delivery efficacy (Scheller et al.)
2008	THUNDER & FEMPAC show femoropopliteal efficacy vs. PTA
2014	LEVANT I/II establish Lutonix performance; U.S. pivotal data
Jan 2015	FDA approval IN.PACT admiral (3.5 μg/mm^2) after IN.PACT SFA
Dec 2018	Katsanos meta-analysis reports late mortality signal
Jan–Mar 2019	FDA letters; caution and investigation; some trials paused
2021	SAFE-PAD (Medicare) shows no mortality difference
Nov 2023	Updated patient-level meta-analysis (Lancet) shows no mortality association
July 2023	FDA: Paclitaxel-coated devices unlikely to increase mortality
2024–2025	RANGER II long-lesion; COMPARE 24-months; TRANSCEND 24-months noninferiority
2025	SWEDEPAD-1 (CLTI) neutral on amputation/mortality; BASIL-3 neutral on AFS
2024–2025	SIRONA interim: SCB noninferior to PCB at 12 months; SELUTION SLR registry 3-years durability

Milestones include early femoropopliteal randomized controlled trials (RCT; THUNDER/FEMPAC), U.S. device approvals from IN.PACT, LEVANT, and ILLUMENATE programs, the 2018–2019 mortality signal and FDA advisories, and subsequent large-scale analyses culminating in the July 2023 FDA communication. Recent readouts include COMPARE, TRANSCEND, and SIRONA, alongside national randomized programs (SWEDEPAD-1/-2, BASIL-3)

AFS amputation-free survival, *CLTI* chronic limb-threatening ischemia, *DCB* drug-coated balloon, *FDA* Food and Drug Administration, *PCB* paclitaxel-coated balloon, *RCT* randomized controlled trial, *SCB* sirolimus-coated balloon, *SFA* superficial femoral artery, *PTA* plain balloon angioplasty

22.5 DCB Performance in CLTI and the Revival of the Mortality Signal

With the safety debate largely resolved, attention shifted toward whether DCB improve outcomes in patients with chronic limb-threatening ischemia (CLTI). The early DCB trials focused primarily on patients with Rutherford class 2–3 (claudication), with rare inclusion of class 4 (ischemic rest pain) and no patients with class 5–6 (tissue loss) [12, 15]. Despite demonstrating superior patency and lower reintervention rates in these populations, it was unclear if these findings would translate to CLTI, where vessel patency does not consistently correlate with limb outcomes [53].

The evidence gap was addressed by two large, randomized trials published in 2025. SWEDEPAD 1 enrolled 2355 patients with Rutherford class 4–6 CLTI undergoing infrainguinal endovascular therapy and randomized them to paclitaxel-coated versus uncoated devices [54]. After a median follow-up of 2.7 years, there was no significant difference in major amputation (7.1 vs. 6.6 events per 100 person-years; HR, 1.05; 95% CI 0.87–1.27) or all-cause mortality (6.2 vs. 6.0 events per 100 person-years; HR, 1.04; 95% CI 0.92–1.17).

In parallel, the BASIL-3 trial (Bypass versus Angioplasty in Severe Ischaemia of the Leg) randomized 481 patients with CLTI requiring femoropopliteal or tibial revascularization to plain

balloon angioplasty with or without bare metal stenting (PBA ± BMS), drug coated balloon angioplasty with or without bare metal stenting (DCB ± BMS), or drug eluting stenting (DES) [55]. At a median follow-up of 2.5 years, amputation-free survival (AFS) did not differ between groups (AFS failure: 66% PBA ± BMS vs. 60% DCB ± BMS; adjusted HR, 0.84; 97.5% CI 0.61–1.16; DES vs. PBA ± BMS HR, 0.83; 97.5% CI 0.60–1.15). There were no differences in secondary outcomes including reintervention rates or quality of life. These findings were corroborated by the SAFE-PAD registry, a nationwide Medicare analysis of 168,553 patients, nearly half with CLTI, which showed no difference in major amputation or long-term mortality between drug-coated and uncoated devices (9-year mortality 76% vs. 78%; adjusted HR, 0.98; 95% CI 0.97–0.99) [45].

In contrast to these neutral results observed in CLTI, the SWEDEPAD 2 trial, which enrolled patients with meeting Rutherford 1–3 criteria, found that use of paclitaxel-coated balloons and stents for femoropopliteal artery interventions was associated with a higher all-cause mortality at 5 years compared to uncoated devices (HR 1.47; 95% CI 1.09–1.98; $p = 0.010$), although this difference was not sustained over the entire median follow-up of 7.1 years [56]. The trial's mortality curves diverged at approximately 2 years and persisted through 5 years, mirroring the late mortality signal first reported in the 2018 Katsanos meta-analysis. However, there was no difference in disease-specific quality of life, reintervention, or major amputation rates between groups. The mechanism underlying this transient mortality signal remains uncertain. Hypotheses such as systemic paclitaxel toxicity, distal drug-particle embolization, or other off-target effects lack supporting biologic or epidemiologic evidence, and no dose-response relationship or clustering of specific causes of death has been demonstrated [57].

22.6 Emerging Sirolimus-Based Platforms and Adjunctive Imaging Technologies

Sirolimus-coated DCB have emerged as an alternative to paclitaxel-based devices for the treatment of femoropopliteal artery disease [57, 58]. Sirolimus offers a pharmacologic advantage through its cytostatic inhibition of smooth muscle cell proliferation via mTOR blockade, providing a wider therapeutic window than paclitaxel, which is cytotoxic. However, because sirolimus is less lipophilic, tissue absorption and retention are reduced compared to paclitaxel, necessitating the use of phospholipid nanocarriers and amphiphilic formulations to enhance vascular wall penetration and sustained local release. A summary of currently available DCB platforms, including drug dose and excipient technology, is provided in Table 22.3.

The first-in-human SELUTION SLR trial provided the early evidence of safety and efficacy for sirolimus-coated DCB [59]. At 6 months, primary patency by duplex ultrasound was 88.4% and freedom from angiographic binary restenosis was 91.2% in patients with symptomatic femoropopliteal disease, with no major safety concerns. Similar results were observed in the SELUTION SFA Japan trial, a prospective multicenter study of 134 patients, which reported a 12-month primary patency rate of 87.9% and freedom from CD-TLR of 97.0%, with no device or procedure-related deaths [60]. Longer-term outcomes from an all-comers registry further supported the durability of sirolimus DCB, demonstrating 3-year primary patency of 74.7% and freedom from CD-TLR of 85.3% [61].

The SIRONA trial, an ongoing RCT comparing sirolimus and paclitaxel DCB in femoropopliteal disease, reported 12-month primary patency of 73.8% with sirolimus DCB versus 75.0% with paclitaxel DCB (difference −1.2%, noninferiority $p = 0.022$), with similar safety and functional outcomes between the two [62, 63]. Additional ongoing randomized trials such as SirPAD and LIMES are evaluating sirolimus DCB in broader infrainguinal and CLTI populations, focusing on endpoints including major adverse limb events,

Table 22.3 Summary of contemporary DCB platforms used for femoropopliteal intervention, listing manufacturer, nominal drug dose density, and excipient or coating technology

Name of DCB	Maker	Drug and dose	Excipient
IN.PACT Admiral	Medtronic	Paclitaxel 3.5 μg/mm^2	Urea
Ranger	Boston Scientific	Paclitaxel 2 μg/mm^2	TransPax (citrate-ester)
Stellarex	Philips (Spectranetics)	Paclitaxel 2 μg/mm^2	Polyethylene glycol (PEG) 8000
Lutonix 035	BD/Bard	Paclitaxel 2 μg/mm^2	Polysorbate-sorbitol
SurVeil	Surmodics/Abbott	Paclitaxel 2 μg/mm^2	PEG-based microcrystalline coating
LEGFLOW	Cardionovum	Paclitaxel 3 μg/mm^2	Shellac resin
SELUTION SLR (SCB)	Cordis (MedAlliance)	Sirolimus 1 μg/mm^2	Phospholipid blend with PLGA polymer (microreservoirs)
MagicTouch PTA (SCB)	Concept Medical	Sirolimus 1.27 μg/mm^2	Phospholipid nanocarrier platform

Sirolimus-coated balloons (SCBs) are shown with their dose densities and carrier platforms
DCB drug-coated balloon, *PCB* paclitaxel-coated balloon, *SCB* sirolimus-coated balloon, *PEG* polyethylene glycol, *PTA* percutaneous transluminal angioplasty, *SFA* superficial femoral artery

amputation, and mortality [64, 65]. The results of these trials will be critical to establishing the comparative effectiveness, durability, and long-term safety of sirolimus-based DCB relative to paclitaxel-coated systems.

22.7 Role of Intravascular Ultrasound in DCB Optimization

Growing evidence supports the use of intravascular ultrasound (IVUS) as an adjunct to endovascular therapy for peripheral artery disease (PAD). By allowing precise measurement of vessel and lumen diameters, IVUS facilitates accurate device sizing, balloon expansion, and assessment of lesion morphology. Earlier studies comparing IVUS-guided versus angiography-guided revascularization yielded inconsistent findings, largely due to heterogeneity in lesion location and device type (DCB, BMS, DES), and procedural strategy [66–69]. However, large retrospective cohort studies have reported that IVUS-guided revascularization is associated with improved primary patency and lower rates of major adverse limb events, acute limb ischemia, and major amputation [70, 71].

More recently, in a multicenter Korean trial of femoropopliteal DCB angioplasty, IVUS guidance was associated with higher technical success and improved postprocedural ankle-brachial index [72]. This translated into higher 12-month primary patency (83.8% vs. 70.1%; $p = 0.01$) and freedom from CD-TLR (92.4% vs. 83.0%; $p = 0.02$) compared with angiography alone. In a 2-year follow-up study by the same investigators, these benefits proved durable, with higher freedom from CD-TLR (87.4% vs. 78.0%; HR, 0.46; 95% CI 0.24–0.88; $p = 0.02$), along with greater sustained clinical (82.4% vs. 71.2%; $p = 0.02$) and hemodynamic improvement (74.8% vs. 61.0%; $p = 0.01$) compared with angiography guidance [73].

The mechanism underlying the improved outcomes with IVUS guidance is postulated to involve more accurate vessel sizing—typically measuring diameters about 1 mm larger than angiography—which enables better lesion preparation, more complete dilation, and uniform drug delivery [74]. Although this mechanistic rationale is supported by emerging data, high-quality randomized evidence on IVUS remains limited

[75]. Broader clinical adoption has been slowed by cost, reimbursement differences, and the lack of standardized procedural protocols, but IVUS is increasingly recognized as a promising tool to enhance the precision and durability of peripheral endovascular therapy [76].

22.8 Future Directions

DCB therapy for SFA intervention continues to evolve through advances in pharmacology, device design, and procedural technique. PCBs remain the standard of care, demonstrating superior patency and lower TLR rates compared with plain angioplasty, though uncertainty persists in complex lesions and high-risk subsets [13, 77]. The Society for Cardiovascular Angiography and Interventions (SCAI) endorses DCB as a preferred endovascular strategy for suitable femoropopliteal disease while emphasizing the need for continued refinement of device design and patient selection [19, 20].

Sirolimus-based DCB have emerged as a promising alternative. By exerting a cytostatic effect, sirolimus offers a wider therapeutic margin than paclitaxel. Early registries have shown high primary patency, low TLR, and an acceptable safety profile, but available data remain limited to short- and medium-term follow-up [57, 76–79]. Ongoing randomized studies, including SirPAD, LIMES, Magical SFA/BTK and SELUTION SFA/BTK, will clarify comparative performance of sirolimus DCB, particularly in the below-the-knee and CLTI populations where evidence remains limited [64, 65].

Procedural optimization remains central to durable outcomes. Residual stenosis, small vessel caliber, and advanced Rutherford classification are established predictors of treatment failure [80, 81]. Lesion preparation with atherectomy, scoring, or lithotripsy may enhance drug uptake in heavily calcified or long lesions [76, 82]. Randomized data also support IVUS guidance, which improves vessel sizing and luminal gain and reduces reintervention. Broader adoption, however, will require cost-effective implementation and standardized imaging protocols.

Ongoing innovation focuses on improving drug transfer efficiency and mechanical performance. Plaque-modification tools, spot-stenting, and bioresorbable scaffolds are being explored to balance luminal durability with minimal implant burden. Disease- and anatomy-specific device design informed by high-resolution imaging, computational modeling, and registry data may further personalize therapy. Together, advances in drug formulation, coating technology, and procedural precision are converging toward more durable and individualized DCB therapy [83–86].

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23 Drug-Coated Balloons for the Treatment of Below-the-Knee Disease

Marco Frazzetto and Bernardo Cortese

23.1 Introduction

Although often overshadowed by coronary and cerebrovascular disease, peripheral arterial disease (PAD) is a widespread systemic atherosclerotic disorder affecting over 200 million people globally and occurring disproportionately in older adults, individuals with diabetes, and those with current or prior tobacco exposure [1]. Nevertheless, PAD remains relatively underrecognized, even though it confers a cardiovascular risk comparable to—or exceeding—that of other vascular beds, including mortality [2]. The clinical spectrum culminates in chronic limb-threatening ischemia (CLTI)—defined by ischemic rest pain, persistent ulceration, or gangrene—with prevalence in the general population around 0.32% [3]. CLTI carries a severe prognosis, marked by high rates of major amputation, functional decline, and all-cause mortality [4]. With global population aging and the continuing rise in diabetes, the burden of PAD and CLTI is expected to increase further, underscoring their importance as clinical and public-health priorities.

Most individuals with CLTI exhibit multilevel disease, and infrapopliteal arterial involvement is present in over 70% of cases [5]. Restoring perfusion to the foot is closely linked to ulcer healing and prevention of limb loss [6–8]. Below-the-knee (BTK) revascularization remains technically demanding: Tibial vessels are long as segment and small in caliber, frequently heavily calcified, leading to complex procedure of revascularization. Even with contemporary techniques and apparent procedural success, restenosis and repeat interventions are common [9]. No strategy has proven clearly superior; reported patency and limb-salvage rates vary widely across published endovascular approaches [10–12]. Within this landscape, drug-coated balloons (DCB)—evaluated alongside stents and other platforms—have been explored as implant-free options aimed at improving patency and limb outcomes in BTK disease.

23.2 Rationale and Clinical Evidence for DCB in BTK Arteries

Local delivery of antiproliferative agents with DCB offers a way to address the limitations of standard angioplasty and permanent scaffolds in

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this complex operational setting. During a single inflation, DCB couple the mechanical lumen enlargement of angioplasty with short-duration transfer of drug to the arterial wall, thereby achieving immediate gain without leaving a metallic implant. The therapeutic goal is to blunt neointimal proliferation, reduce restenosis, and limit repeat revascularization [13]. By avoiding stent placement, DCB therapy also eliminates stent-specific risks—such as fracture and in-stent restenosis—and may decrease downstream costs. Preclinical and clinical studies in the superficial femoral and popliteal vascular beds have shown that DCB delivers pharmacologically meaningful tissue drug levels, underpinning their widespread use in those segments [14–16]. These data, in turn, provide the rationale for evaluating DCB in infrapopliteal disease, where small calibers, diffuse atherosclerosis, and heavy calcification make sustained patency with conventional devices particularly difficult to achieve.

The Drug-Eluting Balloon in Peripheral Intervention for Below-the-Knee Angioplasty Evaluation (DEBATE-BTK, 2013) was the first randomized experience of paclitaxel-coated balloons in the tibial circulation. In this single-center, open-label trial, diabetic patients with CLTI and ≥40-mm stenoses or occlusions in BTK vessels with distal runoff were assigned to DCB or conventional PTA. At 12 months, the primary endpoint—in-segment restenosis assessed predominantly by angiography—favored DCB (27% vs. 74%, $p < 0.001$) [17]. While hypothesis-generating, the study's interpretability is constrained by its single-center design, modest sample size, and reliance on a surrogate angiographic endpoint rather than hard clinical outcomes, which limits generalizability.

The IN.PACT DEEP (published in 2014) is the first large, multicenter, randomized trial (>350 CLTI patients) compared paclitaxel-coated DCB with PTA for BTK angioplasty. At 1 year, DCB did not reduce clinically driven target-lesion revascularization or late-lumen loss, and a numerical excess in major amputation was observed (8.8% vs. 3.6%) [18]. These results prompted withdrawal of the BTK indication for the device and tempered enthusiasm for paclitaxel DCB in tibial interventions. Extended follow-up to 5 years showed no significant between-group differences in TLR (70.9% vs. 76.0%, log-rank $p = 0.406$), major amputation (15.4% vs. 10.6%, $p = 0.108$), or all-cause mortality (39.4% vs. 44.9%, $p = 0.727$). Nonetheless, the study has been criticized for non-standardized wound care, suboptimal follow-up/oversight, and device-related issues (balloon folding/drug availability), which may have influenced outcomes [19].

The Lutonix BTK randomized studies and the Lutonix 014 Global BTK Registry, evaluated the performance of a 0.014″ paclitaxel-coated balloon in this setting; the PTA with this device proved technically feasible and acceptably safe, but showed no consistent advantage over PTA for clinically driven TLR, limb salvage, or amputation-free survival; at 1 year, restenosis and reintervention rates were not different between DCB and PTA, and no clear benefit emerged across registries [20, 21].

The BIOLUX BTK early-phase trials (e.g., BIOLUX P-II and related studies) showed that such paclitaxel-coated balloon achieved high technical success and modest improvements in surrogate patency metrics (late-lumen loss, binary restenosis) vs. PTA, but small samples, short follow-up, and reliance on angiographic endpoints limited conclusions about durable clinical benefit [22–24].

In SINGA-PACLI study, which randomized 129 patients with infrapopliteal disease, the DCB strategy did not improve primary patency, TLR, or limb salvage at one year, and amputation-free survival was numerically higher with PTA [25].

In the IN.PACT BTK pilot trial of 50 CLTI patients—predominantly with infrapopliteal CTO—DCB reduced late-lumen loss only in a subsegmental analysis (0.592 ± 0.944 mm vs. 1.260 ± 0.810 mm; $p = 0.017$), whereas the overall analysis was not significant [26].

The AcoArt II-BTK ($n = 120$; mostly CTOs) reported that DCB therapy resulted in higher primary patency (75% vs. 28.3%; $p < 0.001$), less late-lumen loss (0.43 ± 0.62 mm vs. 0.99 ± 0.55 mm; $p < 0.001$), and greater freedom from CD-TLR at 12 months (91.5% vs. 76.8%; $p = 0.03$), with no mortality difference [27].

In CRURAL DEB, a single-center randomized study of 64 CLTI patients with long, complex BTK lesions, there was no significant difference in primary patency between DCB and PTA (HR 0.64; $p = 0.24$), and secondary outcomes (TLR, amputation-free survival, serious adverse events) were also similar [28].

The largest evidence for the use of paclitaxel-coated balloons in the setting of BTK stems from the SWEDPAD program.

SWEDEPAD 1 was a nationwide, participant-masked, randomized trial testing paclitaxel-coated vs. uncoated balloons or stents in chronic limb-threatening ischemia (Rutherford category 4–6). Across 22 Swedish centers, 2355 patients were randomized after wire crossing and followed through national registries (median ~2.7 years). Infrainguinal segments, including below-the-knee lesions, were eligible. The primary endpoint, ipsilateral major amputation, did not differ between groups (HR 1.05, 95% CI 0.87–1.27). All-cause mortality was likewise neutral (HR 1.04, 95% CI 0.92–1.17). A modest early reduction in target-vessel reintervention with paclitaxel was not durable during extended follow-up [29].

SWEDEPAD 2 evaluated paclitaxel-coated vs. uncoated balloons in patients with intermittent claudication, using the same nationwide, participant-masked, randomization framework (Rutherford category 1–3). A total of 1136 participants were enrolled at 22 centers with long-term linkage to national registries (median follow-up ~7.1 years). The primary endpoint was disease-specific quality of life at one year (VascuQoL-6), which showed no between-group difference. Major amputation and target-vessel reintervention were likewise similar. Overall mortality across the full observation period did not differ materially; however, at five years a higher mortality incidence was observed with paclitaxel-coated devices (HR 1.47, 95% CI 1.09–1.98). The pragmatic design strengthens external validity while highlighting unresolved long-horizon safety questions that warrant cautious interpretation [30].

Across programs and trials, paclitaxel-coated DCB in BTK disease has yielded heterogeneous results, with several neutral trials and few signals of benefit in hard clinical endpoints—sustaining uncertainty about their routine clinical effectiveness (Table 23.1).

Early work on BTK DCB centered on paclitaxel platforms, but sirolimus has recently gained attention as a biologically attractive alternative. Sirolimus is a cytostatic agent that suppresses smooth-muscle proliferation through mTOR pathway inhibition [31]. Experience from the coronary field suggests a broader therapeutic window, a lower risk of distal embolization, and an overall favorable safety profile [32, 33]. In addition, sirolimus is comparatively endothelium-sparing and exhibits anti-inflammatory activity, potentially attenuating leukocyte-mediated processes relevant to restenosis and thrombotic events [34]. These pharmacologic features—together with lingering concerns about paclitaxel efficacy and safety—have prompted renewed interest in sirolimus-based BTK therapy.

The MagicTouch PTA XTOSI pilot (2021) was a prospective, single-arm, single-center evaluation of a sirolimus-coated balloon in 50 high-risk PAD patients, 40% with femoropopliteal and 60% with BTK disease. At 6 months, primary patency was 80% overall (88% femoropopliteal; 74% BTK). By 12 months, freedom from CD-TLR reached 89.7%, amputation-free survival 81.6%, and limb salvage 92.9%, accompanied by improvements in toe pressures and wound status; mortality and amputation rates were low, with no early safety signal [35]. The 3-year report (2024) described maintained safety and encouraging durability, with high freedom from reintervention and sustained limb salvage across territories [36].

Several pivotal studies are now positioned to define the role of sirolimus balloons infrapopliteally. FUTURE-BTK (NCT04511247) is the first randomized, double-blind trial specifically comparing a sirolimus DCB with conventional angioplasty in BTK arteries. In parallel, the large SIRPAD program (NCT04238546) is designed to provide broader safety and efficacy data across both femoropopliteal and BTK segments. The SELUTION SLR BTK initiative (NCT05055297) evaluates a sustained-release sirolimus platform

Table 23.1 Landmark studies evaluating paclitaxel-coated balloons in below-the-knee artery disease

Study	Year	Design/sample size	Population	Primary endpoint	Key results
DEBATE-BTK	2013	Single-center RCT, $n = 132$	Diabetic CLTI, BTK lesions >40 mm with runoff	Binary in-segment restenosis at 12 months	Restenosis in DCB 27% vs. 74% in PTA ($p < 0.001$)
IN.PACT DEEP	2014	Multicenter RCT, $n = 358$	CLTI, infrapopliteal lesions ≥70%	Clinically driven target-lesion revascularization (CD-TLR) and late-lumen loss (LLL) at 12 months	CD-TLR: DCB 9.2% vs. PTA 13.1%, $p = 0.291$; LLL: DCB 0.61 ± 0.78 mm vs. PTA 0.62 ± 0.78 mm, $p = 0.950$; Major amputation: 8.8% vs. 3.6% (non-significant)
BIOLUX P-II	2015	Multicenter RCT, $n = 72$	PAD or CLTI, Single or sequential de novo or restenotic lesions in the infrapopliteal arteries ≥30 mm	Target-lesion primary patency at 6 months	Patency loss was 17.1% in the DCB group vs. 26.1% in the PTA group ($p = 0.298$)
Lutonix Global BTK Registry	2018	Multicenter registry, $n = 314$	CLTI, ≥70% stenosis or occlusion of one of the native BTK arteries below the tibial plateau and above the tibiotalar joint, inflow treatment allowed	Freedom from clinically driven target-lesion reintervention (fTLR) at 6 months	fTLR at 6 months was 87.9%
AcoArt II–BTK	2020	Prospective, multicenter RCT, $n = 120$	CLTI, primary stenosis >70% infrapopliteal arteries	Primary patency and late-lumen loss (LLL) at 6 months, clinically driven target-lesion reintervention (CD-TLR) at 12 months	Primary patency 75% for DCB vs. 28.3% for PTA, $p < 0.001$; LLL 0.43 ± 0.62 mm for DCB vs. 0.99 ± 0.55 mm for PTA, $p < 0.001$; CD-TLR 91.5% for DCB vs. 76.8% for PTA, $p = 0.03$
SINGA-PACLI	2021	Prospective, randomized, two-center, double-blind superiority trial, $n = 138$	CLTI, ≥50% stenosis or occlusion of at least one native infrapopliteal artery, total lesion length ≤200 mm	Target-lesion primary patency in the absence of clinically driven target-lesion revascularization or surgical bypass	Primary patency 43% in the DCB group vs. 38% in the PTA group ($p = 0.480$)

(continued)

Table 23.1 (continued)

Study	Year	Design/sample size	Population	Primary endpoint	Key results
IN.PACT BTK	2022	Prospective, multicenter, randomized pilot study, $n = 50$	CLTI, Total occlusions of infrapopliteal arteries with total lesion length ≥40 mm	Late-lumen loss (LLL) at 9 months	LLL = 0.892 ± 0.774 mm for DCB vs. 1.312 ± 0.720 mm for PTA, $p = 0.070$ in a classic analysis, and 0.592 ± 0.944 mm for DCB vs. 1.260 ± 0.810 mm For PTA, p = 0.017 in a subsegmental analysis
CRURAL DEB	2025	Single-center, randomized, single-blinded, parallel group, superiority trial, $n = 64$	CLTI, infrapopliteal disease lesion length >2 cm	Primary patency	No significant difference, hazard ratio = 0.64 95% CI = 0.30–1.35, $p = 0.240$
SWEDEPAD 1	2025	Multicenter, randomized, pragmatic, participant-masked, registry-based, $n = 2400$	CLTI (Rutherford 4–6); infrainguinal incl. BTK	Ipsilateral major amputation	No difference vs. uncoated; HR 1.05 (95% CI 0.87–1.27); all-cause mortality HR 1.04 (0.92–1.17)
SWEDEPAD 2	2025	Multicenter, randomized, pragmatic, participant-masked, registry-based trial, $n = 1136$	Intermittent claudication (Rutherford 1–3); infrainguinal	PAD-specific QoL at 1 year (VascuQoL-6)	No QoL difference; 5-year mortality higher with paclitaxel HR 1.47 (1.09–1.98); amputations/ reinterventions neutral

RCT randomized controlled trial, *CLTI* chronic limb-threatening ischemia, *BTK* below-the-knee, *DCB* drug-coated balloon, *PTA* percutaneous transluminal angioplasty, *PAD* peripheral artery disease

with controlled drug kinetics, aiming to improve vascular healing and long-term patency. Collectively, these trials should determine whether sirolimus can mitigate the heterogeneity observed with paclitaxel devices and support a new standard for limb salvage in CLTI.

Given the limited and heterogeneous evidence based to date—and ongoing debate surrounding drug-coated technologies—there is currently no FDA-cleared infrapopliteal indication for DCB in the USA, and these devices are not commercially available for BTK use [37–41]. Consistent with this regulatory position, contemporary guidance in the USA discourages routine infrapopliteal DCB use outside clinical trials or registries, underscoring the need for robust randomized data before widespread adoption.

Disclosures None.

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The Role of Drug-Coated Balloons for the Treatment of Arteriovenous Fistulae

24

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24.1 Introduction

The increasing prevalence of end-stage renal disease (ESRD) in the United States underscores the critical need for effective and durable renal replacement therapies (RRT). Data from the United States Renal Data System 2023 Annual Data Report (ADR) reveals a notable increase in newly diagnosed ESRD patients, from 97,856 diagnosed in 2001 to 135,972 diagnosed in 2021, a 39% increase [1]. Of the patients with incident ESRD in 2021, 83.8% were initiated on hemodialysis (HD) via vascular access in the form of a surgically created arteriovenous fistula (AVF), arteriovenous graft (AVG), or catheter [1]. Of the 808,536 patients in 2021 with ESRD, 58% were on HD and 60.7% of these patients dialyzed via an autogenous AVF, the preferred long-term vascular access route due to its superior resistance to infection, lower rates of thrombosis, and greater patency rates compared to AVG [1–5].

However, AVF do suffer from suboptimal patency rates, with data from the 2023 ADR demonstrating that at 1 year a cumulative incidence of 40.6% for loss of primary unassisted patency after initiation of HD with an AVF [1]. Maintaining patency of such access is paramount for the long-term survival of this population and represents a formidable challenge for the interventionist. The dominance of hemodialysis via AV as the primary RRT in the United States highlights the need for efficacious and minimally morbid interventional modalities to maintain and re-establish patency. While open surgical intervention has its merits and indications in the maintenance of AVF, endovascular intervention offers a less invasive and less morbid means of AVF maintenance and rescue, especially important in the comparably ill ESRD population.

The Nation Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend percutaneous balloon angioplasty (PTA) as the primary intervention for stenotic AVF and AVG lesions, which is the predominate etiology of compromised access patency [6, 7]. Restenosis post-angioplasty, however, remains a frustrating and common occurrence with the use of PTA alone in the treatment of dialysis access malfunction. Drug-coated balloons (DCB), coated with antiproliferative agents intended to inhibit restenosis, have emerged as promising alternatives to conventional PTA [8].

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In the following chapter, the mechanism, performance, clinical evidence, and practical applications of drug-coated balloon angioplasty for dialysis access maintenance will be explored, with emphasis on DCB role in improving outcomes for patients undergoing hemodialysis via an AVF or AVG.

24.2 Intimal Hyperplasia and DCB

The success of long-term hemodialysis vascular access is often undermined by venous stenosis that, due to hemodynamic derangements, precipitates thrombosis and ultimately access failure [9]. Intimal hyperplasia (IH) secondary to vascular injury, typically at the surgically manipulated juxta-anastomotic segments (Fig. 24.1a–c) or areas of extrinsic anatomic compression (cephalic arch), is widely believed to be the causative factor of pathologic stenosis [10, 11]. Histologic examination of stenotic specimens demonstrates an accumulation of proliferative vascular smooth muscle cells (VSMC) in the venous intima (Fig. 24.1d, e), thus impairing flow through the circuit and increasing the risk of malfunction or a thrombotic event [5, 12]. This environment ultimately leads to thrombosis of the circuit, thereby resulting in access failure and compromised dialysis capabilities.

In the treatment of stenosed circuits, DCB combine the immediate mechanical benefits of traditional PTA to achieve luminal expansion with the prolonged therapeutic effect of localized antiproliferative drug delivery to the vessel walls. Typically, DCB are coated with Paclitaxel, a cytostatic drug that interferes with VSMC proliferation and migration—two critical processes that contribute to intimal hyperplasia and, consequently, restenosis. Upon inflation and wall apposition, paclitaxel is transferred locally and taken up by—VSMCs, wherein it exerts its antiproliferative effects to inhibit intimal hyperplasia induced by the traumatic mechanical dilation.

24.3 Clinical Evidence Supporting the Use of DCB for AV Fistulae

24.3.1 Patency

Maintaining the patency of vascular access for hemodialysis is paramount as failure of a circuit adds to ESRD patients' morbidity and mortality. Patency is consequently a metric of significant importance and interest in the evaluation of interventions that aim to maintain and preserve vascular access.

A preponderance of the recent meta-analyses and systematic reviews comparing AVF patency rates after PTA and DCB suggests superior results with DCB. While conventional PTA does succeed in restoring patency in the immediate post-dilation time period, it has limited, time-dependent effectiveness in maintaining long-term patency with high restenosis rates. Patency rates of AVF after PTA at 6 months post-treatment are reported to be 49–56%, declining overtime to approximately 20% at 12-months post-treatment [13–15]. In contrast, DCB patency rates are reported between 71% and 82% at 6 months post-treatment, though too suffer from a time-dependent loss of effectiveness with a rate of 35–44% at 12-months post-treatment [8, 13, 16–18]. See Tables 24.1 and 24.2 for relevant RCTs and systematic reviews and their results.

In the context of access patency, DCB, as compared to PTA, demonstrate superior performance at both 6- and 12-months post-treatment and should be considered an effective tool in optimizing AVF access maintenance.

24.3.2 Reduction in Reintervention Rates

A compelling advantage of DCB in dialysis access management is their potential to significantly reduce the need for repeat interventions. Reintervention is a concern in the ESRD population as the need to reintervene imposes a physical and emotional burden and increases the risk of complications in a fragile, medically complex

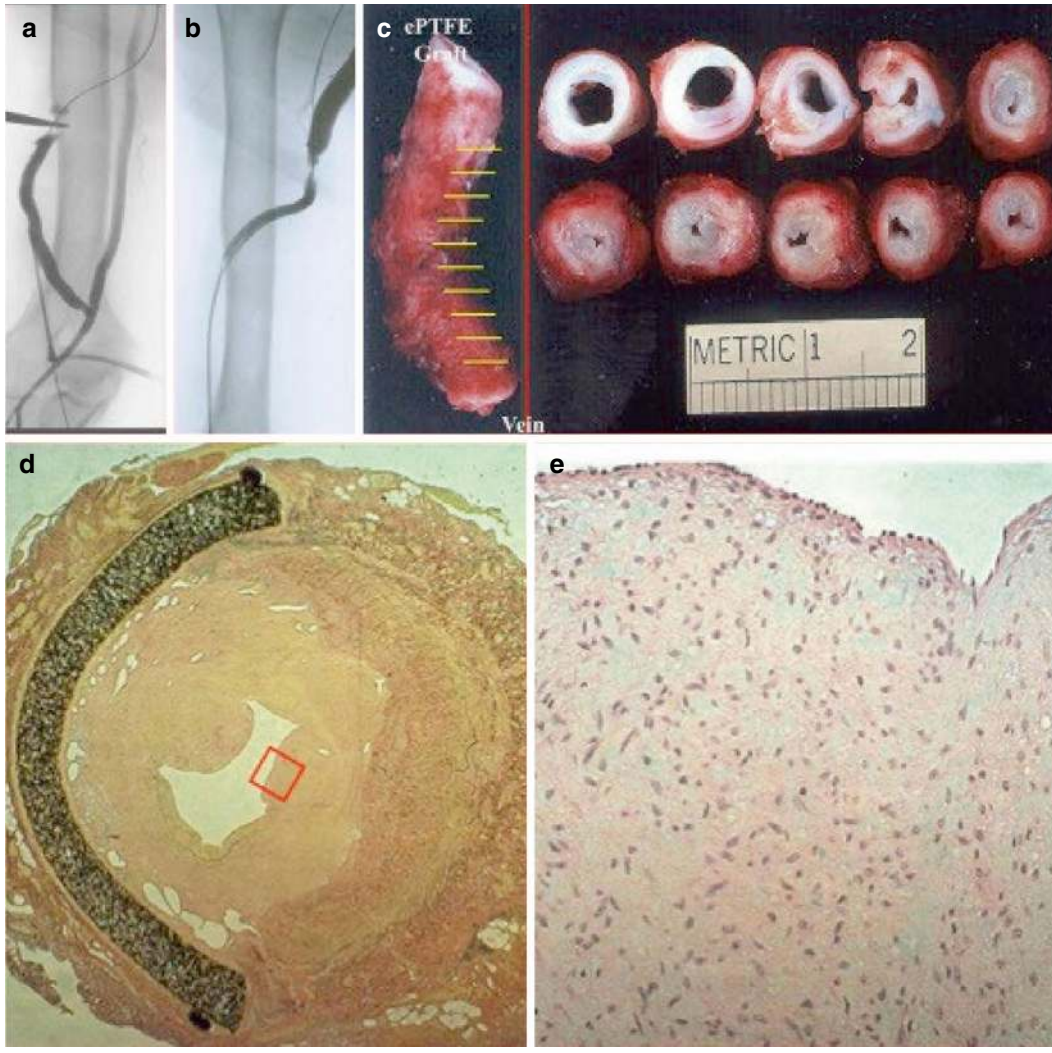


Fig. 24.1 (**a**, **b**) Fistulograms showing a stenosis at the polytetrafluoroethylene graft anastomosis to the basilic vein. (**c**) A gross specimen from a different patient showing thickening of the vein to graft anastomosis. Hematoxylin and eosin stain (**d**) at 10× magnification demonstrating a thickened neointima and (**e**) at 40× magnification (red box in **d**) showing increased cellular proliferation. ePTFE, expanded polytetrafluoroethylene. (Adapted from "Intimal hyperplasia in vascular grafts and the progression to secondary stenosis," by Brahmbhatt et al. [10]. © 2015 Elsevier Inc. Licensed under CC BY 4.0. Source: https://www.sciencedirect.com/science/article/pii/S0085253815000939)

patient population. Healthcare costs, too, are escalated by the need for frequent reintervention.

As discussed previously, traditional PTA, though effective in restoring patency in the short-term, is associated with high rates of restenosis at medium- and long-term timescales [13]. DCB therapy has been shown to reduce restenosis events, thereby increasing the interval between interventions and providing longer periods of durable vascular access [19, 23]. Lookstein et al. [8] demonstrated that DCB significantly reduced the need for target lesion revascularization (TLR) within 12 months compared to PTA alone. Patients in the DCB group had a reintervention rate of approximately 29% at 1 year,

Table 24.1 Representative randomized controlled trials (RCTs) comparing DCB versus PTA alone, including relevant characteristics of each trial

Randomized controlled trials (RCT)			
Author/title	Single or multicenter	Number of patients	Results
Lookstein et al. Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas [8]	Multicenter	330	DCB maintained 82.2% patency vs. 59.5% for PTA over 6 months.
Pang et al. Randomized Controlled Trial for Paclitaxel-coated Balloon versus Plain Balloon Angioplasty in Dysfunctional Hemodialysis Vascular Access: 12-month Outcome from a Nonsponsored Trial [14]	Single center	96	DCB reduced restenosis to 56.5% vs 81.1% and access failures to 45% vs 66.7% compared to PTA.
Irani et al. Hemodialysis Arteriovenous Fistula and Graft Stenoses: Randomized Trial Comparing Drug-eluting Balloon Angioplasty with Conventional Angioplasty [15]	Multicenter	200	DCB angioplasty improved lesion primary patency and reduced restenosis rates at 6 months.
Trerotola et al. Drug Coated Balloon Angioplasty in Failing AV Fistulas: A Randomized Controlled Trial [16]	Multicenter	285	Paclitaxel-coated balloons did not significantly improve 180-day patency compared to conventional angioplasty.
Kitrou et al. Drug-eluting versus plain balloon angioplasty for the treatment of failing dialysis access [17]	Single center	98	DCB angioplasty improved 1-year target lesion primary patency to 35% vs. 5% for PTA.
Swinnen et al. Multicenter randomized blinded control trial of drug-eluting balloon vs Sham in recurrent native dialysis fistula stenoses [19]	Multicenter	177	DCB reduced restenosis and increased freedom from reintervention at 12 months.
Yin et al. Efficacy and Safety of Paclitaxel-Coated Balloon Angioplasty for Dysfunctional Arteriovenous Fistulas: A Multicenter Randomized Controlled Trial [20]	Multicenter	218	DCB treatment achieved 65% primary patency at 6 months vs. 37% for control.
Katsanos et al. Paclitaxel-coated balloon angioplasty vs. plain balloon dilation for the treatment of failing dialysis access: 6-month interim results from a prospective randomized controlled trial [21]	Single center	40	DCB treatment achieved 70% patency vs. 25% in BA at 6 months.

DCB drug-coated balloon, *BA* Balloon angioplasty

compared to over 40% in the PTA group. This reduction in reintervention rates translates into fewer hospital visits, less exposure to procedural risks, and a decrease in the cumulative financial costs associated with maintaining dialysis access.

24.3.3 Technical and Safety Profiles

Both DCB and PTA achieve high procedural success rates, with no significant differences demonstrated in immediate post-procedural outcomes between the two approaches [20].

DCB are safe to use in the maintenance of dialysis access. Several studies have demonstrated that DCB are non-inferior to conventional PTA in terms of safety, with similar rates of serious adverse events within the 30-day post-procedure period. Trerotola et al. [16] demonstrated noninferiority in safety in their 2018 randomized trial of DCB compared to PTA. This finding was further confirmed by Lookstein et al. [8], in their prospective

Table 24.2 Representative systematic reviews and meta-analyses comparing DCB versus PTA alone, including relevant characteristics of each trial

Systematic reviews and meta-analyses			
Paper primary author/title	Number of studies	Number of total patients	Results
Yan Wee et al. A systematic review and meta-analysis of drug-coated balloon versus conventional balloon angioplasty for dialysis access stenosis [13]	6	483	DCB angioplasty showed higher 12-month patency rates compared to PTA.
Kennedy et al. Drug-Coated Balloon Angioplasty in Hemodialysis Circuits: A Systematic Review and Meta-Analysis [18]	12	908	DCB improved patency in AVF at 3, 6, 12, and 24 months.
Dinh et al. Mortality After Paclitaxel-Coated Device Use in Dialysis Access: A Systematic Review and Meta-Analysis [22]	8	685	Paclitaxel-coated devices showed no difference in all-cause mortality compared to uncoated balloons.

randomized trial including 330 patients, which presented a 4.2% and 4.4% rate of serious adverse event (AVF occlusion, thrombosis, site complication) for DCB and PTA, respectively. Additional studies have also confirmed the favorable safety profile of DCB with low rates of minor complications and no increase in mortality [13, 17, 22, 24].

DCB, though superior in terms of maintenance of AVF patency compared to PTA, do admittedly feature a time-dependent loss of effectiveness and restenosis necessitating additional intervention. Repeated treatments and exposure to paclitaxel, albeit locally as opposed to systemically, have been demonstrated in retrospective analyses to not increase the risk of adverse events and maintains a consistent safety profile across multiple interventions [25].

24.3.3.1 Cost-Effectiveness of DCB for AV Fistulae

The economic implications of managing ESRD are substantial, especially considering the chronic nature of the condition and intensive resources required for ongoing treatment. In this context, the cost-effectiveness of DCB and PTA in maintaining dialysis access is a critical consideration for both healthcare providers and policymakers.

The initial costs of DCB are higher than those of conventional PTA due to the specialized drug coating and the technology involved in their production, leading to higher per-procedure costs. This difference in upfront expenditure raises concerns among healthcare providers, particularly in resource-constrained settings, where immediate costs are a major consideration in decision-making. However, while the initial expense of DCB is higher, this can be viewed in the context of the overall cost of care for ESRD patients. The upfront investment in DCB may be justified by the potential for long-term economic benefits they offer, as it relates to reduced reinterventions, fewer hospitalizations, and decreased procedural risks. Each avoided reintervention not only saves on the direct costs of the procedure itself but also reduces the associated costs of hospitalization, anesthesia, post-procedural care, and the management of potential complications. This reduction translates to potentially significant cost savings when multiplied across the large population of ESRD patients requiring dialysis access maintenance. Over time, the cumulative savings from fewer interventions can be more than offset the initial higher costs of DCB, likely making them a cost-effective choice in the long run.

Additional potential long-term savings from dialysis access DCB therapy among ESRD patients arise not only from the direct costs avoided through fewer procedures but also from the broader economic benefits of improved patient outcomes and reduced healthcare resource utilization. In the context of ESRD management,

where the economic burden is substantial and rising, DCB present a potential cost-effective solution that aligns with the goals of improving patient care while optimizing healthcare expenditures. By shifting the focus from short-term cost considerations to long-term value, DCB offer a pathway to more sustainable and effective management of dialysis access, ultimately reducing the economic burden of ESRD. This is an area that would benefit from further research.

24.4 Take Home Messages

The utilization of DCB therapy in dialysis access preservation represents a significant advancement in the management of vascular access for patients with ESRD. As the prevalence of ESRD continues to rise, the need for effective and durable solutions to maintain AVF patency becomes increasingly critical. DCB therapy offers a promising alternative to traditional PTA, addressing one of the most challenging aspects of dialysis access—restenosis due to neointimal hyperplasia.

The clinical evidence supporting the use of DCB is compelling. Multiple studies and meta-analyses consistently demonstrate that DCB provide superior patency rates compared to PTA alone, particularly at both 6- and 12-months post-intervention. This is a crucial benefit for ESRD patients, as maintaining access patency directly correlates with improved morbidity and mortality outcomes. By reducing the frequency of restenosis, DCB not only extend the functional lifespan of a dialysis access but also decrease the need for repeated interventions, which can be both physically taxing for patients and financially burdensome for healthcare systems.

The reduction in reintervention rates observed with DCB use is another key advantage, highlighting their role in enhancing the quality of life for patients who require long-term hemodialysis. The ability of DCB to reduce the frequency of reinterventions translates to fewer hospital visits, decreased procedural risks, and ultimately, a more stable and reliable dialysis access over time.

Furthermore, the safety profile of DCB has been rigorously evaluated, with studies demonstrating that DCB are noninferior to PTA alone in terms of safety. The comparable rates of serious adverse events between DCB therapy and PTA alone within the critical 30-day post-procedure period reinforce the viability of DCB as a safe alternative for AVF maintenance. This favorable safety profile, coupled with the efficacy in prolonging patency, positions DCB therapy as a well-rounded and reliable option for vascular access management.

Despite these advantages, it is important to acknowledge the time-dependent loss of effectiveness associated with DCB. While DCB outperform PTA in the short- to mid-term, their efficacy does diminish over time, which underscores the need for ongoing innovation and optimization in this field. Continued research and development are essential to further enhance the durability of DCB and to explore new drug formulations or delivery methods that could extend their therapeutic benefits.

In summary, DCB therapy represent a significant innovation in the management of dialysis access, offering superior patency rates, reduced reintervention needs, and a solid safety profile. As our understanding of their mechanisms and clinical applications continues to evolve, DCB therapy is poised to become a cornerstone in the treatment of AVF stenosis, ultimately improving the long-term outcomes for patients with ESRD. The integration of DCB therapy into clinical practice has certainly been a positive advancement in the contemporary management of dialysis access, offering a sustainable and patient-centered approach to maintaining the lifelines of those dependent on hemodialysis.

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25 Translational Application of Drug-Coated Balloons to the Treatment of Vasculogenic Erectile Dysfunction

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25.1 Introduction

Erectile dysfunction (ED) of vascular origin is increasingly recognized as a sign of widespread endothelial dysfunction, often occurring alongside atherosclerotic disease in other vascular beds. Among patients with vasculogenic ED, a significant number have obstructive lesions of the internal pudendal artery (IPA) and penile arteries. Endovascular treatment, initially inspired by coronary and peripheral interventions, has evolved from simple balloon angioplasty to the use of drug-coated balloons (DCB), which deliver an antiproliferative drug to prevent neointimal hyperplasia and restenosis without leaving a permanent scaffold.

The "leave nothing behind" paradigm, initially validated in small-vessel coronary and in-stent restenosis settings, provides an attractive conceptual and technical framework for penile circulation, characterized by small-caliber, highly dynamic vessels prone to flow-limiting recoil and diffuse disease. By ensuring homogeneous antiproliferative drug delivery without mechanical caging, DCB may preserve physiological vasomotion and facilitate positive vascular remodeling—a particularly relevant aspect in erectile hemodynamics [1].

Since the first reports of pudendal and penile artery angioplasty for ED over a decade ago, technological advances have paralleled the evolution of coronary DCB, with newer sirolimus-eluting platforms now supplementing paclitaxel-based technologies. However, robust clinical evidence in the ED field remains limited to small pilot series, case reports, and early prospective registries.

In a significant subset of men with vasculogenic ED, flow-limiting atherosclerotic stenoses in the erectile arteries—most often the IPA, common penile artery, and distal penile branches—impair cavernosal blood flow. This "arteriogenic ED" is appealing for percutaneous revascularization when lesions are short, focal, and proximally

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located enough to supply large portions of the penis. Modern imaging and physiological techniques, such as selective angiography with or without intravascular imaging, are used to identify localized disease and rule out widespread microvascular dysfunction.

This chapter aims to provide an updated and critical review of the use of drug-coated balloon angioplasty for vasculogenic erectile dysfunction, incorporating lessons learned from coronary and peripheral applications.

25.2 Pathophysiological and Technical Background

25.2.1 Vascular Anatomy and Pathophysiology

The IPA branches from the anterior division of the internal iliac artery and supplies blood to the muscles and erectile tissues of the external genitals, as well as parts of the anal and urogenital regions. Vasculogenic ED mainly results from reduced arterial inflow due to stenosis or blockage of the IPA, its terminal branches (such as the common penile artery, cavernosal artery, and dorsal artery), or the internal iliac artery. These vessels are small—typically 2.5–3 mm proximally and 1.5 mm or less distally—and are highly responsive to vasomotor signals. Like coronary microcirculation, even slight narrowing of the lumen can significantly decrease blood flow and impair erectile function.

In this context, endovascular therapy aims to restore normal penile blood flow while minimizing mechanical trauma. However, traditional stent placement in the pudendal or penile arteries is technically challenging and can cause flow problems or late stent fracture from repeated movement during erection. As a result, a stent-free approach using DCB has become a physiologically and anatomically appropriate alternative.

25.2.2 The DCB Concept and Drug-Delivery Mechanics

Drug-coated balloons consist of a semi-compliant angioplasty balloon coated with an antiproliferative drug (such as paclitaxel or a limus analogue, mainly sirolimus), combined with an excipient that enhances drug transfer and retention within the vessel wall. When inflated (usually at nominal pressure for 60–90 s), the drug rapidly diffuses through the intima, delivering a high local concentration and a sustained antiproliferative effect without leaving polymeric residues.

The DCB platform was first introduced in the early 2000s, following the demonstration of paclitaxel's effectiveness in preventing neointimal growth after balloon injury in animal models [2]. Later clinical validation was provided by the PACCOCATH and PEPCAD series for coronary ISR [3, 4] and by DCB ARC [5, 6]. These studies laid the technical groundwork that was later adapted for use in peripheral and coronary arteries.

25.2.3 Parallels Between Coronary and Penile "Small Vessels"

The average diameter of the distal internal pudendal or common penile artery is comparable to that of a coronary branch, less than 2.5 mm. In both settings, stent placement can lead to excessive neointimal growth and is technically challenging. Experience with small-vessel coronary disease has shown that DCB is safe and effective compared with drug-eluting stents (DES)—as demonstrated in the PICCOLETO II trial [7], BASKET-SMALL 2 [8], and RESTORE SVD China [9]. These findings support similar approaches in pelvic-penile revascularization, where vessel size, blood flow, and restenosis mechanisms are comparable.

25.2.4 Lesion Assessment and Procedural Planning

High-resolution imaging with digital subtraction angiography (DSA), computed tomographic angiography (CTA), or intravascular ultrasound (IVUS) can help identify the culprit stenosis and guide balloon sizing. According to DCB ARC 2025 [5, 6], procedural success requires:

1. Full balloon expansion observed in two orthogonal projections.
2. Final residual stenosis is less than 30% by quantitative analysis.
3. Absence of flow-limiting dissection or thrombosis (TIMI 3 flow).
4. No need for bailout stenting in a "leave-nothing-behind" strategy.

The limited elasticity and tortuosity of pelvic arteries require careful handling to avoid dissection, while prolonged inflation times (up to 4 minutes) improve drug absorption. In fact, optimal lesion preparation remains the key predictor of a successful outcome [10]. It is also important to wait at least 2-3 minutes to assess elastic recoil of the treated segment.

25.3 Pharmacological Platforms: Paclitaxel vs. Sirolimus

25.3.1 Mechanistic Differences and Pharmacokinetics

The antiproliferative drugs used in DCB belong to two pharmacological families with distinct mechanisms of action and physicochemical properties. Paclitaxel is a highly lipophilic, cytotoxic compound that stabilizes microtubules by binding to the β-subunit of tubulin, thereby preventing cell division and migration of vascular smooth muscle cells. Its lipophilicity enables rapid tissue uptake and prolonged retention, even after brief balloon–vessel contact. This property, together with its ability to inhibit neointimal hyperplasia, explains its early adoption as the reference drug for coronary and peripheral DCB. Sirolimus, on the other hand, is a macrolide that acts cytostatically. It binds to FKBP12, thereby inhibiting the mammalian target of rapamycin (mTOR) and halting the cell cycle at the G1-S transition. Although less lipophilic than paclitaxel, sirolimus offers a wider therapeutic window and lower cytotoxicity and may promote better vascular healing profiles [11].

The pharmacological differences between these two drugs lead to distinct coating requirements and pharmacokinetics. While paclitaxel can be delivered in crystalline form with rapid absorption, sirolimus requires specialized excipients or micro-reservoir systems to ensure adequate transfer and controlled elution [12–14] (Fig. 25.1).

25.3.2 Role of Excipients and Coating Morphology

Drug alone cannot ensure effective, long-lasting absorption into the vessel wall. Excipients—such as tiropramide, urea, shellac, dextran, or magnesium stearate—help control drug release, tissue retention, and downstream particulate loss. Early paclitaxel balloons (e.g., Sequent Please, IN.PACT Falcon) used hydrophilic excipients such as iopromide to promote rapid transfer during 60-s inflation.

More recently, advances in crystalline coatings and micro-reservoir technologies have improved sirolimus delivery. For example:

- Magic Touch™ (Concept Medical) uses nanolute microdroplets for deep penetration and slow release lasting up to 60 days (the balloon used for ED—i.e., Magic Touch ED—has the same pharmacokinetics as the coronary counterpart) [15].
- Selution SLR™ (MedAlliance) combines biodegradable polymer micro-reservoirs with sirolimus at 1 μg/mm^2 and provides controlled-release kinetics for up to 90 days.
- Bingo™ (Yinyi Biotech) is an SCB that incorporates magnesium stearate and butylated hydroxytoluene as excipients to improve bioavailability and stability.

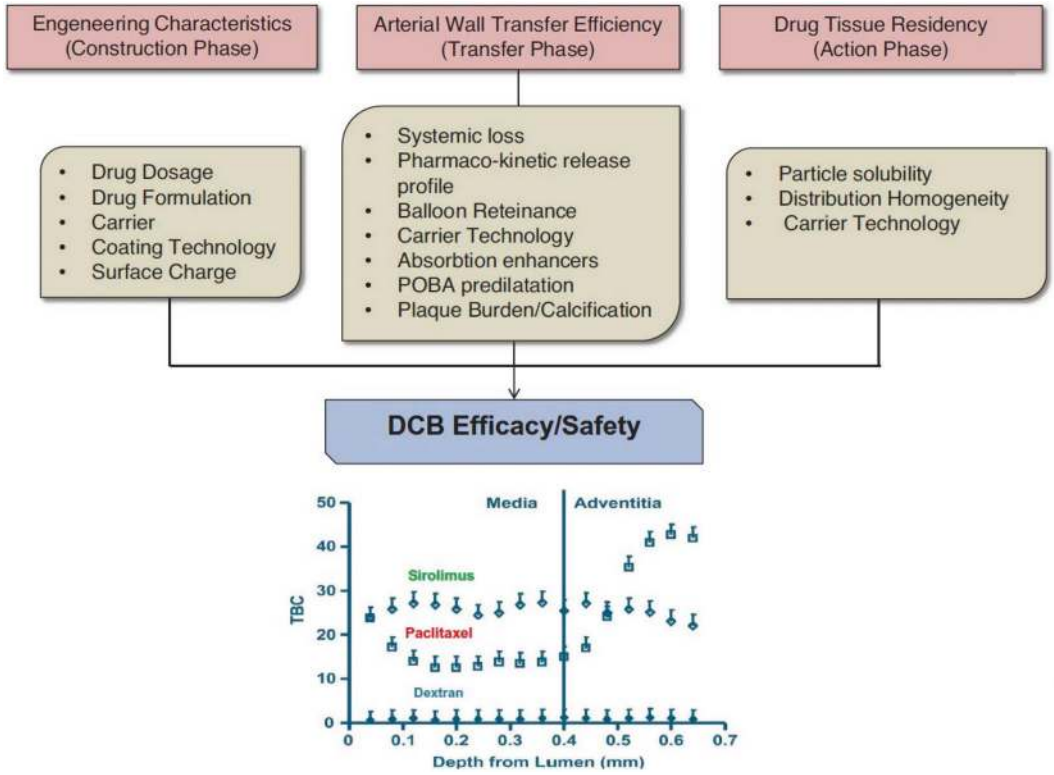


Fig. 25.1 Engineering, Patient and Procedural Variables that may influence the results of current DEBs

These innovations represent a new generation of "limus-based" balloons with more physiologic drug kinetics, potentially promoting improved endothelial recovery and reduced inflammation compared with paclitaxel devices [16].

25.3.3 Comparative Pharmacological Performance

Preclinical and clinical studies have compared paclitaxel- and sirolimus-coated balloons across vascular territories. In coronary ISR, both drugs showed similar efficacy in reducing late lumen loss [17], whereas in small vessel disease, sirolimus-coated balloons achieved variable results, with a lower angiographic performace but a similar physiological outcome during angiographic follow-up, like in the recently published PICCOLETO VI study [18–20].

The potential benefit of sirolimus lies in its cytostatic rather than cytotoxic effect, which reduces endothelial injury and inflammation. These considerations are important when applying this technology to penile arteries, where maintaining microvascular health is crucial.

25.3.4 Safety Considerations

Concerns about paclitaxel-related mortality in peripheral artery disease, raised by an early meta-analysis [21], were later contradicted by more comprehensive analyses and have not been confirmed in coronary applications. Large registries and patient-level data show no increased risk of death or aneurysm formation following coronary paclitaxel DCB angioplasty [22].

Given the delicate pelvic vascular environment and erectile tissue perfusion, sirolimus-

coated balloons may offer an improved safety profile, with reduced distal embolization and lower risk of downstream toxicity. Nonetheless, comparative long-term data in the ED setting remain limited and require prospective validation.

25.4 Translational and Clinical Evidence of Drug-Coated Balloon Angioplasty in Erectile Dysfunction

25.4.1 Rationale and Evolution from Coronary to Pelvic–Penile Circulation

The development of DCB technology stems from the goal of revascularization techniques that restore vessel patency without permanently leaving a metal scaffold. Originally designed for coronary in-stent restenosis, the "leave nothing behind" concept was gradually shown to be effective in more complex cases—such as small-vessel disease, bifurcations, and diffuse coronary atherosclerosis—and ultimately led to its application in the pelvic–penile circulation.

The hemodynamic and anatomic similarities between the coronary and pudendal-penile arterial systems are notable [23]. Both systems feature small-caliber vessels (2–3 mm proximally, <2 mm distally), high-resistance flow, and a marked susceptibility to restenosis. Additionally, the penile arteries exhibit strong vasomotor reactivity, making them particularly vulnerable to mechanical distortion or flow disturbance after stent implantation. In this context, DCB angioplasty offers the theoretical benefit of uniform antiproliferative drug delivery while preserving native vasomotion and avoiding the potential risks of chronic inflammation, late thrombosis, or fracture associated with metallic stents.

The translation of DCB therapy to treat vasculogenic ED follows a logical physiological progression: a technology designed to preserve vessel structure and function in small, dynamic coronary segments is naturally suited to the penile circulation, where similar constraints exist. The pathophysiological basis of ED (microvascular endothelial dysfunction, reduced nitric oxide bioavailability, and flow-limiting stenosis of the pudendal–penile arteries) mirrors that of coronary microvascular disease.

The foundation for endovascular treatment of erectile dysfunction was laid by the *ZEN trial* [24], which demonstrated the safety and feasibility of zotarolimus-eluting stent placement for internal pudendal artery stenoses. Among 30 men with pharmacologically resistant erectile dysfunction, percutaneous stent revascularization achieved 100% procedural success, significant increases in cavernosal peak systolic velocity (+22 cm/s at 6 months), and meaningful clinical improvements in 59–70% of patients. Despite these positive results, angiographic binary restenosis occurred in 34% of cases, and the permanent metallic scaffold limited natural vasomotion—prompting the development of the stent-free drug-coated balloon approach.

25.5 Evidence from Coronary Small-Vessel and Bifurcation Disease Experience

Clinical validation of DCB in small-vessel coronary disease is essential for applying this technology to the pelvic–penile area. Small coronary arteries, typically ≤2.75 mm in diameter, exhibit excessive neointimal growth after stenting, leading to higher restenosis rates and technical challenges in achieving optimal expansion. Multiple randomized controlled trials have shown that DCB angioplasty can deliver outcomes equivalent to, and sometimes better than, those of drug-eluting stents in these lesions.

The BELLO trial first demonstrated significantly lower 6-month late lumen loss (0.08 mm vs. 0.29 mm, $p = 0.001$) with paclitaxel-coated balloon angioplasty compared to a paclitaxel-eluting stent in vessels ≤2.8 mm, with comparable rates of target lesion revascularization (TLR) and major adverse cardiac events (MACE). The BASKET-SMALL 2 trial [8] confirmed these findings in 758 patients, showing non-inferiority of DCBs to sec-

ond-generation DES at 1-year follow-up (MACE 7.3% vs. 7.5%). The RESTORE SVD China trial [9] supported these results in an Asian population, demonstrating non-inferior in-segment diameter stenosis (29.6% vs. 24.1%) and similar clinical outcomes at 12 months.

Further progress was achieved with the introduction of sirolimus-coated balloons. Trials such as TRANSFORM I [25] and TRANSFORM II [26] are analyzing a new nanocapsule technology that enables controlled sirolimus release. Although TRANSFORM I failed to demonstrate the non-inferiority of sirolimus-eluting balloons compared with paclitaxel-eluting balloons, the results of TRANSFORM II in de novo vessel disease are eagerly awaited in 2026 to see if this technology can match stents in de novo lesions in an all-comer population.

In bifurcation disease, DCB helps preserve side branches without adding extra stent layers. The PEPCAD-BIF trial [27] and the DEBSIDE study [28] showed reduced late lumen loss and positive remodeling when DCB was used on side branches after main-vessel stenting. Comparable hybrid strategies—proximal DES placement combined with distal DCB use—have also proven effective for long or diffuse or bifurcation coronary lesions [29, 30, 31]. Overall, these findings support the use of DCB as a safe and effective option for small-caliber, bifurcated, and moving vascular areas, offering rapid drug transfer, even coverage of the inner vessel wall, and minimal risk of mechanical damage.

25.5.1 Clinical Application of Drug-Coated Balloons in Erectile Dysfunction

Early clinical experience in penile revascularization was established by the PERFECT trial. It was the first prospective human study to assess simple balloon angioplasty for isolated penile artery stenoses in patients with refractory erectile dysfunction. Procedural success was achieved in all 23 treated arteries, with no major adverse events and an average IIEF-5 score increase of 5.2 points at 6 months. The subsequent PERFECT-2 study [32] built on these findings with quantitative CTA follow-up, reporting a 91% procedural success rate and sustained clinical improvement in 50% of patients at 1 year. However, binary restenosis occurred in about 40% of treated lesions, underscoring the need for more durable drug-based technologies. The field has since shifted toward sirolimus-eluting platforms. The SUASION Registry [33] is the first multicenter, prospective study evaluating the Magic Touch sirolimus DCB with nanotechnology in men with angiographically confirmed pudendal or penile artery disease and refractory ED. The procedural protocol followed coronary standards—mandatory pre-dilation, balloon inflation for 60–90 s, and 4 weeks of dual antiplatelet therapy (DAPT). Enrollment has been completed, and a 1-year follow-up will be presented in 2026. Once completed, the registry will provide the first structured evidence that sirolimus DCB is both safe and effective for restoring penile perfusion.

Early angioplasty-only studies reported improvements in erectile function in about 60% of cases, but restenosis remained a challenge. Paclitaxel- and sirolimus-eluting balloons were later introduced to mitigate neointimal proliferation. Preliminary trials (e.g., SUASION, PERFECT) confirmed safety and a positive clinical signal, although randomized data remain limited. Ongoing RCTs are currently evaluating DCB and SEB outcomes for restenosis and IIEF-EF improvement. Notably, the PERFECT-SELUTION FIM trial (*NCT05362994*) aims to confirm these preliminary findings in larger populations with standardized endpoints and long-term follow-up. Additionally, innovative case reports have investigated combining DCB angioplasty with cell-based therapy, showing potential synergistic effects for vascular regeneration [34]. Although most studies are small, non-randomized, and heterogeneous in device platforms and lesion sites, current guidelines from andrology and sexual medicine in Italy have endorsed the efficacy of DCB angioplasty for treating erectile dysfunction [35]. Nonetheless, long-term durability, standardized endpoints, and large RCTs are still lacking, and current results

should primarily be viewed as hypotheses-generating for focal, proximal arteriogenic ED.

25.5.2 Synthesis and Future Directions

Although still limited in scale, the current body of evidence consistently supports the feasibility, safety, and functional effectiveness of DCB angioplasty for vasculogenic ED. Procedural success rates are high, complications are rare, and improvements in erectile function (measured objectively by IIEF-5 and PSV) are clinically significant. The sirolimus-based technology appears particularly well suited to this vascular area, combining durable antiproliferative effects with good biological tolerance. Data from coronary and peripheral trials further reinforce its position as the next-generation DCB platform.

However, several challenges remain:

- Small patient populations and varying inclusion criteria limit generalizability.
- Short follow-up periods preclude definitive conclusions about long-term patency.
- Non-standardized endpoints (hemodynamic, angiographic, functional) hinder comparability across studies.

Future research should adopt standardized definitions and endpoints recommended by the DCB-ARC [5, 6], including quantitative measures of lesion success (<30–40% residual stenosis), angiographic follow-up, and functional metrics such as ΔIIEF-5 and ΔPSV. Large, randomized, multicenter trials comparing sirolimus DCB with paclitaxel DCB or DES implantation in well-characterized ED populations are needed. Incorporating intravascular imaging (IVUS/OCT) and advanced Doppler assessment may further improve patient selection and procedural outcomes. Ultimately, adopting DCB angioplasty for erectile dysfunction exemplifies a translational innovation: a therapy originally designed for the coronary microcirculation that is now emerging as a minimally invasive, restorative approach to male sexual health.

25.6 Technical Considerations for Pudendal and Penile Drug-Coated Balloon Angioplasty

25.6.1 Patient Selection and Pre-procedural Evaluation

Proper patient selection is key to successful DCB angioplasty for vasculogenic ED. Candidates should present with:

1. Documented vasculogenic erectile dysfunction refractory to phosphodiesterase-5 inhibitors or intracavernosal agents.
2. Angiographically significant stenosis (≥70%) or flow-limiting lesions in the internal pudendal, common penile, or cavernosal arteries.
3. Lack of widespread atherothrombotic disease prevents selective access.
4. Preserved cavernosal tissue function, confirmed by penile Doppler ultrasonography showing PSV <25 cm/s, an intact veno-occlusive mechanism (PDV > 5 cm/sec), and normal cavernous bodies opacification during selective CO_2 angiography.

Non-invasive imaging techniques, such as CTA or magnetic resonance angiography (MRA), provide an anatomical roadmap for procedural planning, whereas selective DSA remains the gold standard for lesion characterization. Pre-procedural optimization of risk factors, including smoking cessation, lipid control, and antiplatelet therapy, is recommended and aligns with contemporary standards for peripheral revascularization.

25.6.2 Access, Equipment, and Vessel Preparation

Endovascular treatment is performed via contralateral femoral access, typically with a 6 Fr guiding catheter (e.g., JR4 or Left Mammary Artery shape). Selective cannulation of the internal iliac artery and subsequent navigation into the IPA require careful manipulation to prevent vessel

spasm or dissection. Systemic anticoagulation with unfractionated heparin (70–100 IU/kg) is administered to maintain the activated clotting time above 250 s.

25.6.3 Lesion Preparation: A Determinant of Success

Lesion preparation is essential for successful DCB angioplasty and includes:

- Complete balloon expansion in at least two orthogonal views.
- Residual stenosis of 30% or less prior to DCB deployment.
- No flow-limiting dissection or thrombus formation (TIMI 3 flow).

Pre-dilatation should be performed with semi-compliant or non-compliant balloons matched 1:1 to the vessel diameter, inflated for 30–60 s. In calcified or fibrotic lesions, scoring or cutting balloons may facilitate plaque modification, reduce elastic recoil, and ensure uniform drug uptake. For severe calcification resistant to conventional dilation, intravascular lithotripsy or atherectomy may be considered before DCB use, although experience in pudendal vessels remains limited. These technical steps, extensively validated in coronary DCB angioplasty, are equally applicable in the pelvic–penile area, where lesion morphology and vessel size closely resemble those of distal coronary branches.

25.6.4 Device Selection

The DCB should be selected based on the vessel's reference diameter and lesion length.

- Diameter: 1:1 ratio with the reference vessel diameter in the coronary district (typically 1.5–3.0 mm in pudendal–penile arteries).
- Length: at least 2 mm longer than the prepared lesion at both ends to prevent geographic miss.
- Inflation: apply nominal pressure for 60–90 s to ensure complete drug transfer.

SCB such as Magic Touch ED™ (the only DCB with CE mark for ED) and Selution SLR™ are preferred for their favorable pharmacokinetic profile and prolonged tissue retention. Both devices use carrier matrices (micro-reservoirs or nanolute droplets) that ensure sustained sirolimus release for 60–90 days, supporting vessel healing and reducing restenosis.

25.6.5 Technique

1. After adequate lesion preparation with semi or non-compliant balloons, the DCB is advanced to the target site under fluoroscopic guidance.
2. Inflation is applied slowly to the nominal pressure, maintaining full contact for 60–90 s.
3. Post-dilatation or stent implantation should be performed only if there is severe recoil or dissection [36].
4. Care should be taken to avoid multiple balloon inflations at the same site, as repeated contact can remove the drug coating.

The operator should visually confirm complete balloon expansion and ensure there is no contrast hang-up. If residual stenosis exceeds 30% or a flow-limiting dissection is evident, bailout stenting with a small-profile drug-eluting stent may be considered. However, in the "leave-nothing-behind" approach, stent implantation should be the exception rather than the rule (Fig. 25.2).

25.6.6 Imaging Guidance and Follow-Up

Although not yet standardized in ED interventions, IVUS and OCT can provide valuable insights into vessel size, plaque burden, and post-procedure lumen gain (Fig. 25.3). As proposed

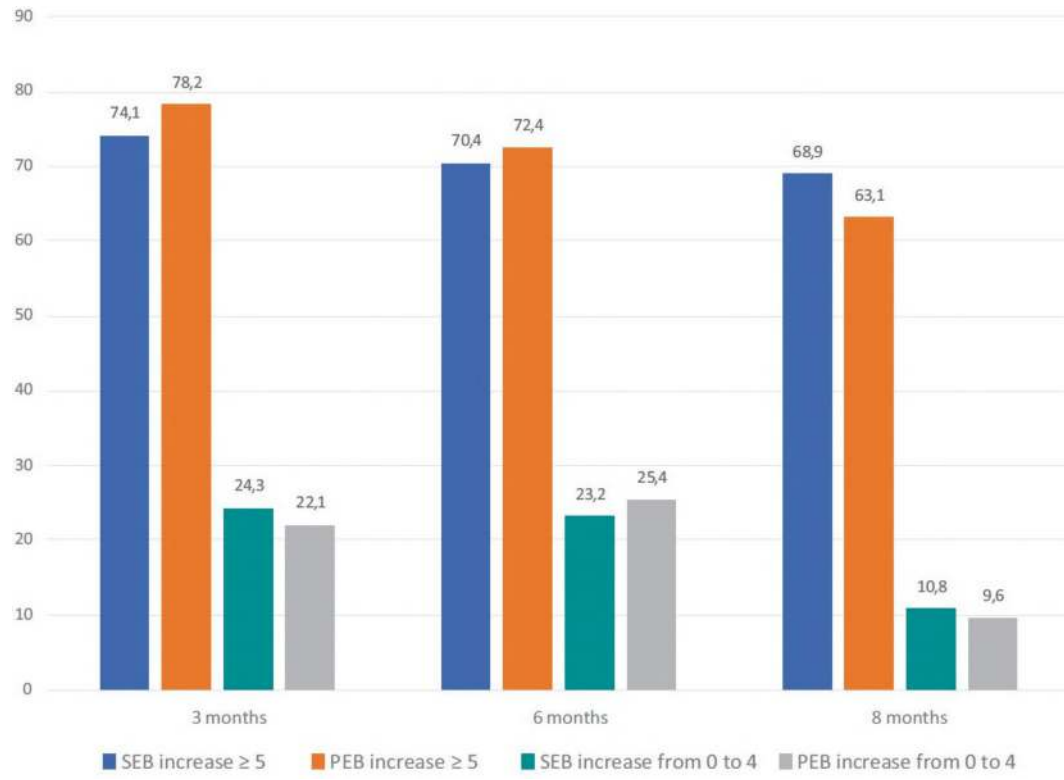


Fig. 25.2 Treatment success referred to minimal clinical improvement in the IEF-5 score between SEB (N = 56) and PEB (N = 138) in a consecutive personal series of patients affected by arteriogenic DE at 8 months follow-up (personal communication, ANMCO Congress 2020)

by the DCB ARC 2025 [5, 6], intravascular imaging should be used to confirm the following:

- Adequate lesion expansion.
- Intimal integrity (lack of deep dissections);
- Absence of thrombus or slow flow;

Accurate drug-delivery coverage of the treated segment.

Future trials should incorporate these modalities to enhance procedural consistency and ensure adherence to the ARC's angiographic success criteria.

25.6.7 Post-procedural Follow-Up

With no permanent scaffold, vessel healing after DCB angioplasty generally occurs quickly. In stable patients, a brief 4-week course of dual antiplatelet therapy, followed by single antiplatelet therapy (Aspirin or Clopidogrel), may be adequate. Clinical follow-up should include:

- Penile Doppler ultrasonography at 3 and 6 months to assess PSV and flow symmetry.
- IIEF-5 reassessment to measure functional improvement.
- Optional CTA or angiographic evaluation at 6–12 months for research protocols.

Re-intervention criteria include symptomatic recurrence with PSV less than 25 cm/s or imaging evidence of over 70% restenosis. In such cases, repeat DCB angioplasty may be considered, as drug re-exposure has been shown to be safe based on coronary experience.

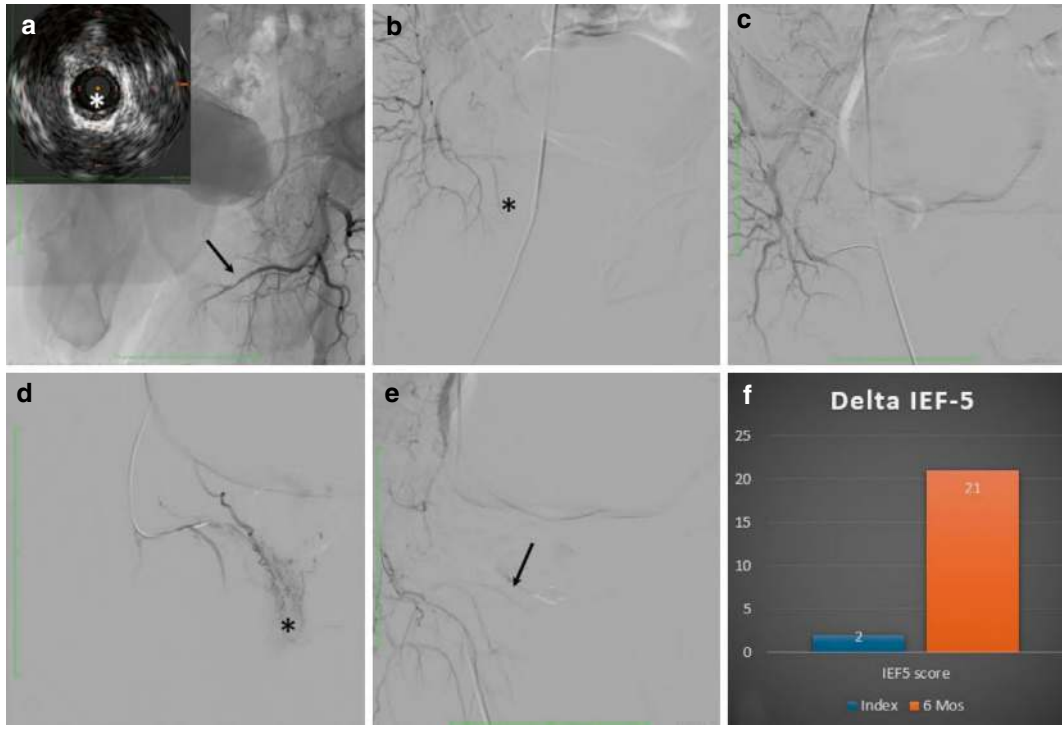


Fig. 25.3 *Panel A:* Right 45° oblique projection of the left pudendal artery showing minimal irregularities in the distal segment 4B (arrow). IVUS (upper left insert) shows a minimal fibrotic plaque in this segment (asterisk). *Panel B.* The left 45° oblique projection from the same patients shows a complete occlusion of the segment 4B (asterisk) of the right pudendal artery. *Panel C* shows advancement of 0.014 wire within a microcatheter. *Panel D* demonstrates contrast injection through a microcatheter with complete opacification of the right cavernous body (asterisk). *Panel E* shows Final angiographic result after DCB angioplasty with a Magic Touch^{ED} sirolimus-eluting balloon after 3 min of inflation. *Panel F:* Improvement of IIEF score at 6 months from the index procedure

25.6.8 Safety Considerations and Pitfalls

The safety profile of DCB angioplasty in the pudendal and penile arteries is favorable, with no reported instances of perforation, distal embolization, or ischemic complications in published series. However, several procedural details require attention.

- Avoid over-dilation: Excessive balloon oversizing can cause dissection or vessel rupture.
- Prevent geographic miss: Ensure complete coverage of the prepared segment, as uncovered areas are at risk for restenosis.
- Minimize contrast load: Because the vessel caliber is small and multiple injections are required, limiting contrast is crucial to prevent spasm and endothelial injury.
- Manage spasm: Intra-arterial nitroglycerin or verapamil can prevent vasospasm during selective pudendal engagement.

In the unlikely event of a dissection that impairs flow, prolonged inflation of a non-compliant balloon or provisional stenting might restore patency. Importantly, no increase in adverse events has been linked to sirolimus-coated balloons compared with paclitaxel devices in both coronary and pelvic.

25.7 Safety, Limitations, and Future Directions

25.7.1 Safety Profile of Drug-Coated Balloon Angioplasty

Based on available evidence and consensus guidelines, Table 25.1 outlines the key points and the optimal technical approach for pudendal and penile DCB angioplasty.

The safety record of DCB angioplasty in both coronary and peripheral settings is excellent, and early experiences in the pelvic–penile circulation are consistent with this pattern. From a pharmacological perspective, sirolimus-based coatings offer an added margin of safety. Compared with paclitaxel, sirolimus is cytostatic rather than cytotoxic, promoting controlled inhibition of smooth muscle growth without hindering endothelial recovery. Unlike early concerns in the peripheral artery literature regarding paclitaxel exposure, no evidence of increased mortality has emerged in the coronary or penile settings. Modern low-dose formulations (2–3 μg/mm^2) and optimized excipients have significantly reduced distal drug embolization and tissue toxicity. Overall, current data support the excellent safety and tolerability of DCB angioplasty for treating vasculogenic erectile dysfunction.

Table 25.1 Practical recommendations for pudendal and penile DCB angioplasty

Step	Technical recommendation
1. Diagnostic Assessment	Symptoms lasting >6 mos and not responding to PDEF5 treatment for more than 6 mos IIEF score <10 PSV <25 cm/s after 10 mcg of alprostadil injection
2. Lesion identification	Angiographic stenosis ≥70% or PSV <25 cm/s after 10 mcg of alprostadil injection
3. Pre-dilation	Non-compliant/scoring balloon, 1:1 sizing, 30–60 s
4. DCB selection	Diameter 1:1 to vessel, length ≥ lesion +4 mm
5. Inflation	90-200s at nominal pressure
6. DAPT	4 weeks (then SAPT)
7. Success criteria	Residual stenosis ≤30–40%, TIMI 3 flow, no dissection
8. Follow-up	Doppler + IIEF-5 at 3–6 mos; optional imaging at 12 mos

DAPT dual antiplatelet therapy, *DCB* drug-coated balloon, *IIEF* International Index of Erectile Function, *PSV* peak systolic velocity, *SAPT* single antiplatelet therapy, *TIMI* Thrombolysis in Myocardial Infarction

25.7.2 Procedural and Anatomical Challenges

Despite its favorable safety profile, DCB angioplasty of the pudendal and penile arteries poses unique anatomical and technical challenges.

- Vessel tortuosity and small caliber: The internal pudendal artery and its branches often measure less than 2 mm distally, making wire manipulation and balloon navigation challenging. Soft-tip 0.014″ coronary guidewires and low-profile balloons are recommended.
- Vasospasm: The penile arterial bed is highly responsive; intra-arterial nitroglycerin or calcium-channel blockers should be used liberally.
- Geographic miss: Because these arteries are short and branch, accurate lesion coverage is essential.
- Dissection and recoil: Excessive dilation pressures or undersized DCB can cause flow-limiting dissections. Operators should aim for gentle pre-dilation and standard inflation pressures, with prolonged contact (≥60 s) to ensure even drug transfer.

A learning curve is unavoidable. Centers with prior coronary DCB experience are better equipped to safely adopt the technique for pelvic interventions. Standardizing procedures, supported by imaging and drug protocols, reduces complication risk and improves reproducibility.

25.7.3 Methodological and Evidence-Based Limitations

The primary limitation of current evidence is the lack of randomized controlled trials focused on erectile dysfunction. Most available data come

from small observational registries, pilot studies, or extrapolations from the coronary literature. As a result, long-term patency and functional durability are not fully established.

Another limitation is the variability in endpoints across studies. While most researchers report improvements in IIEF-5 and PSV, few include standardized angiographic or imaging follow-up. The DCB-ARC has addressed this issue by recently proposing uniform definitions for procedural success and outcome measures (such as target lesion revascularization, late lumen gain or loss, and patient-oriented composite endpoints). Using criteria for procedural success adapted from coronary intervention (residual stenosis ≤30–40%, TIMI 3 flow, no flow-limiting dissection) and standard definitions of outcome measures will be crucial for ensuring comparability and enabling meta-analyses in future research.

The field also has a limited understanding of long-term vascular biology in the penile circulation after DCB therapy. Although coronary studies suggest complete endothelial recovery within 3–6 months, similar evidence in the pudendal arteries is lacking. Systematic follow-up with intravascular IVUS, OCT, and penile Doppler could clarify mechanisms of healing, remodeling, and drug retention.

25.7.4 Future Perspectives

The coming decade should mark a shift from feasibility studies to well-designed, multicenter, randomized trials comparing sirolimus DCB, paclitaxel DCB, and DES implantation in men with angiographically confirmed pudendal or penile artery disease and vasculogenic erectile dysfunction. Core endpoints should include functional improvement (ΔIIEF-5 ≥4 points, PSV increase ≥10 cm/s) and freedom from target lesion revascularization at 12 months. Secondary outcomes should focus on the duration of double antiplatelet therapy, safety, and patient-reported satisfaction, as measured by validated questionnaires such as SHIM and EHS [37].

Advances in intravascular imaging and physiology—including IVUS, OCT, quantitative flow ratio (QFR), and angiography-derived FFR—will be essential for accurate lesion characterization and for quantitative assessment of drug distribution, thereby reducing geographic miss. Computational modeling of drug kinetics and wall shear stress in small-caliber arteries may further enhance device design and procedural approaches [38].

Future directions also include regenerative and personalized approaches that combine sirolimus DCB angioplasty with autologous stem cell or platelet-rich plasma (PRP) therapy to improve microvascular recovery [38]. Incorporating endothelial biomarkers and advanced imaging could help identify patients most likely to benefit from this evolving endovascular strategy.

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26 How Will DCB Impact the Revascularization Strategies in the US After Approval for All the Indications?

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26.1 Introduction

Drug-eluting stent (DES) implantation is the most common revascularization strategy for patients undergoing percutaneous coronary intervention (PCI). Nonetheless, considering the non-negligible risks related to the implantation of long and multi-layer stents, drug-coated balloon (DCB) angioplasty has emerged as an alternative approach in certain scenarios [1]. By providing homogeneous antiproliferative drug delivery with no foreign body implantation, DCB offers a "metal free" option that may preserve normal vessel anatomy and function, accelerate arterial healing, potentially favor positive vessel remodeling, and avoid the implantation of multiple layers of stents in case of failure (Table 26.1). Specifically, DCB angioplasty may be preferred for the following scenarios:

1. In-stent restenosis (ISR);
2. Small vessel disease;
3. To avoid a "full metal jacket" in long lesions;
4. For procedural simplification when treating complex lesions such as bifurcations and chronic total occlusions (CTO).

In addition, specific clinical factors that might particularly benefit from DCB angioplasty include patients with high-bleeding risk (given the possibility for a short dual antiplatelet therapy course), diabetes mellitus (often associated with small vessel and diffuse disease, and an increased risk of ISR) or acute coronary syndrome (ACS, where proper vessel size might not be obvious).

In this context, we hereby address limitations of permanent metallic scaffolds, provide a contemporary panorama of DCB usage across the globe, and forecast the potential impact that DCB angioplasty may have on PCI revascularization strategies within the United States, aware that the current European and Asian experiences may shed light on the future of DCB in the US (Fig. 26.1).

26.2 Limitations of Permanent Metallic Scaffold Implantation

DES implantation allows the operator to obtain an immediate, stable result (Table 26.1). This feature contributes to the observation that DES implantation represents today the most com-

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Table 26.1 Pros and cons of a DCB PCI strategy

DCB PCI strategy	
Pros	Cons
May simplify the procedure	Requires specific operator skills
Short or no DAPT	Requires evaluation of coronary dissection
Allows positive vessel remodeling	Less appealing immediate result
Limits stent layers	Needs more supporting studies

DAPT dual antiplatelet therapy, *DCB* drug-coated balloon, *PCI* percutaneous coronary intervention

mon revascularization strategy for patients undergoing PCI. More importantly, in some scenarios, DES implantation mitigates the risk of emergency bypass surgery, myocardial infarction, and sometimes death, as supported by several randomized studies and registries. Nonetheless, limitations to universal DES implantation when performing PCI should be recognized:

1. There is a 2% yearly rate of adverse events following DES implantation. This value increases when dealing with long stents and diabetic patients, and explains the considerable proportion of ISR PCI performed in the United States, estimated to be about 10% of all PCIs [2].
2. Stents restrict positive vascular remodelling and pulsatile function in the treated segment;
3. The concept of stenting from healthy-to-healthy vessels, proposed at the time of short stents, leads to the implantation of very long stents;
4. A suboptimally implanted stent may be deleterious;
5. Stent delivery can be complex, especially in challenging lesion subsets such as bifurcations;
6. ISR may be difficult to treat.

Together, these reasons support the addition of DCB angioplasty within the armamentarium of contemporary PCI.

26.3 Contemporary Worldwide DCB Usage

Since their introduction for coronary use in Europe over 15 years ago, DCB have experienced a gradual increase in adoption across global clinical practices. Although treatment of ISR is currently the only indication for DCB angioplasty in the United States, interest in the development of novel, limus-coated devices and wider experience in the treatment of de novo lesions have contributed to wider, although heterogeneous, adoption of this technology (Fig. 26.2). Indeed, while DCB integration into clinical practice remains in its early stages in most regions in Africa and Latin America, the proportion of PCI procedures including DCB angioplasty has progressively increased in Europe and Asia, with DCB currently used in about 20% of PCIs in Japan. Notwithstanding the general upward trend in utilization of this technology, DCB usage may vary considerably across institutions. Similarly, it is key to realize that penetration of specific DCB technologies varies as well. The experience with SeQuent Please paclitaxel DCB (B. Braun Melsungen, Germany) and Magic Touch sirolimus DCB (Concept Medical, India) has accrued over the past years across more than 50 countries. The recent acquisition of MedAlliance (Nyon, Switzerland) by Cordis (Miami Lakes, FL) and the ongoing investigation of SELUTION sirolimus DCB (Cordis, FL) in large-scale randomized controlled trials for treatment of both ISR and de novo lesions, results of both recently presented at TCT, may further boost DCB penetration [3] (pls see the relative chapter for the primary endpoint presentation at TCT 2025, San Francisco).

26.4 ISR

Traditionally, ISR has been defined as a reduction ≥50% of the luminal diameter (as assessed by coronary angiography) or ≥75% of the reference vessel area (as assessed by intravascular imaging) within the previously stented segment or the vessel segments 5 mm proximal and distal to the stent [4]. It may be the result of multiple coexist-

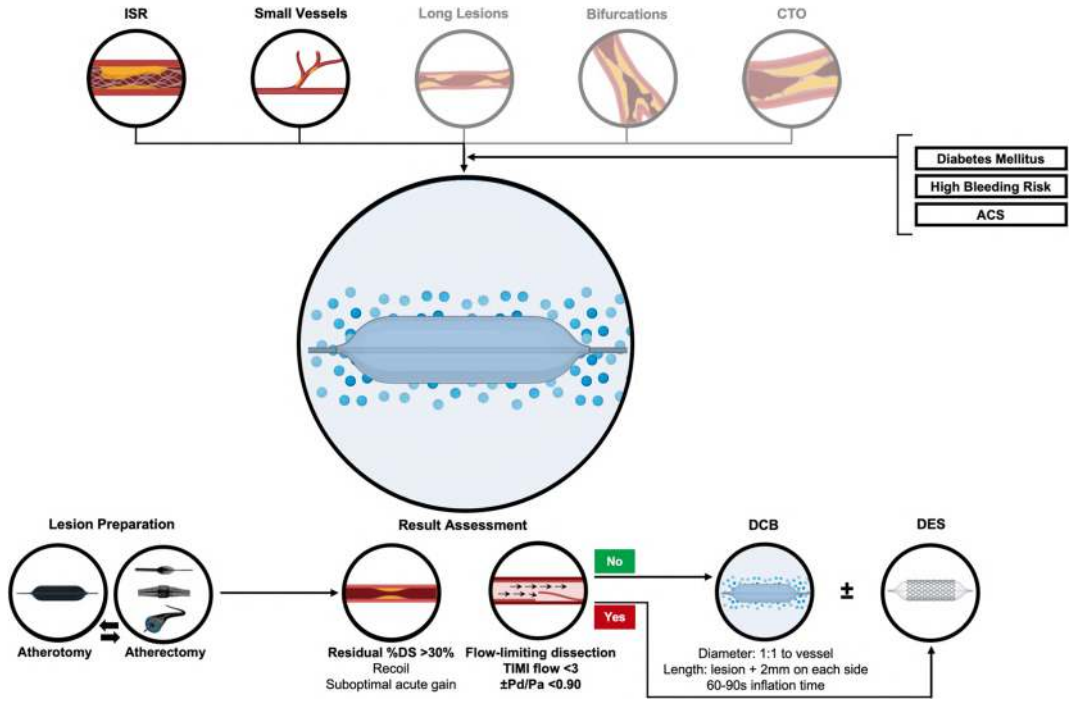


Fig. 26.1 DCB angioplasty: when and how. At the top, current and emerging (in opaque) clinical scenarios for DCB PCI outside the United States are highlighted. Clinical factors supporting the use of this approach are reported within the boxes on the right. At the bottom, a systematic approach to DCB PCI, including lesion preparation, result assessment, and DCB angioplasty and/or stenting, is suggested. Additional factors evaluated during result assessment include symptoms, EKG ischemic alterations, persistent contrast hang-up, and progressive luminal narrowing. ACS acute coronary syndrome, DES drug-eluting stent, DS diameter stenosis, Pd/Pa distal coronary/aortic pressure ratio, TIMI thrombolysis in myocardial infarction

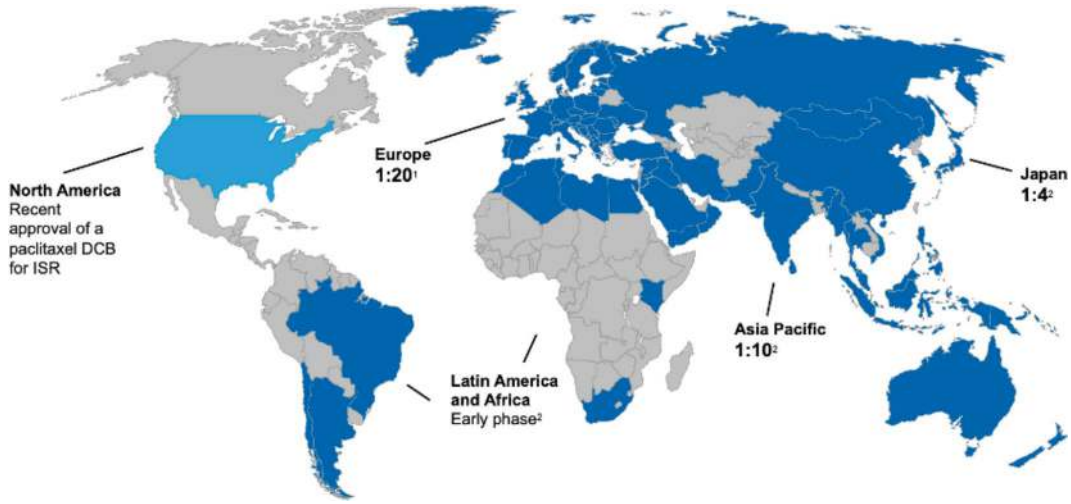


Fig. 26.2 World distribution of a paclitaxel DCB:DES ratio for PCI (early year 2024, a higher usage is to be expected by 2026). The map outlines the penetration of a paclitaxel DCB (SeQuent Please, B. Braun Melsungen, Germany) usage across the globe. Usage of DCB vs. DES for PCI is expressed as DCB:DES ratio. The approved paclitaxel DCB in the United States is AGENT (Boston Scientific, Marlborough, MA). (Figure readapted from B. Braun Melsungen AG. [1]EUCOMED-Data Europe, 2022; [2]EUCOMED-Data, 2022 & Internal Data B. Braun Melsungen AG). DCB drug-coated balloon, DES drug-eluting stent, PCI percutaneous coronary intervention

ing factors, including mechanical factors, such as stent undersizing, underexpansion, or fracture; lesion calcification and geographic miss; and biological factors such as neointimal hyperplasia and neoatherosclerosis. Regardless of the underlying mechanism, ISR remains a challenging lesion subset with a higher risk of adverse events compared to de novo lesions.

The largest supporting evidence for DCB PCI has accrued in ISR. Solid evidence supports angiographic and clinical superiority of DCB vs. balloon angioplasty in both bare metal stent and DES ISR. Such results have recently been corroborated in a multicenter randomized clinical trial (RCT) conducted on 600 patients enrolled in the United States [5]. When compared with DES implantation, DCB angioplasty, on one hand, showed similar safety; on the other hand, it was found to be moderately less effective than DES in terms of target lesion revascularization, a difference driven by patients treated for DES ISR [6]. Nonetheless, considering the excess of long-term adverse events with multi-layer stenting, DCB represents a valid "metal-free" option. In this context, although DCB holds a class I recommendation (level of evidence A) for ISR in European guidelines, the first DCB technology for treatment of ISR in the United States was approved by the Food and Drug Administration on March 1st 2024, representing a new era in the treatment of ISR in the United States. Historically, intravascular brachytherapy (IVBT) has been investigated at the time of bare metal stents for the management of ISR in the United States [7]. Notwithstanding its relative efficacy with respect to other technologies available at the time of study conduction, the absolute residual risk remained quite high [8]. In addition, the marginal evidence available since DES introduction has prevented the common use of this technology in modern practice.

Altogether, this gives us the opportunity to revisit the current treatment strategies available for ISR in the United States, and to forecast the collocation of available and upcoming DCB technologies within the panorama. DCB is particularly attractive in case of relevant side branches emerging from the failed stent, and in patients with bare metal stent, multi-layer or small vessel ISR; on the other hand, DES implantation might be considered a first option in case of stent fracture or geographical miss. One of the most important aspects of DCB PCI is appropriate lesion preparation [9], as the DCB serves the sole purpose of 360° delivery of an antiproliferative drug to the vessel wall. Thus, the operator should keep in mind that the acute gain related merely to stent implantation should be accounted for, and DES implantation might still be preferred in case of suboptimal lumen expansion (i.e. residual diameter stenosis >30%). High-pressure non-compliant, scoring or cutting balloon angioplasty, when feasible, is a reasonable upfront strategy irrespective of the number of stent layers, lesion appearance and underlying mechanism. Nonetheless, should intravascular imaging reveal stent underexpansion as the underlying mechanism, high pressure balloon inflations should be favored. Super non-compliant balloon inflations (at up to 35 atm) and intravascular lithotrispy should be considered in case of resistant calcified lesions. Given the lack of constant radial strength when treating a lesion without stent implantation, such an approach is key in case of intention to treat with DCB, as the effectiveness of DCB angioplasty is not expected to be satisfactory if the *primum movens* of ISR is not resolved. For the same reason, an upfront or cross-over strategy including laser or rotational atherectomy should be considered in case of CTO or diffuse ISR before DCB angioplasty. Considering that studies evaluating DCB for ISR have not often included a large proportion of patients with multi-layer ISR, whether IVBT could potentially hold such a niche indication remains to be established. Coronary artery bypass grafting remains the last resort in presence of recurrent ISR, especially in good surgical candidates with multivessel disease, left main or large proximal epicardial vessel ISR.

26.5 *De novo* Lesions

Within the sphere of de novo coronary artery disease, the evidence for DCB PCI is well established for lesions in small vessels (often defined

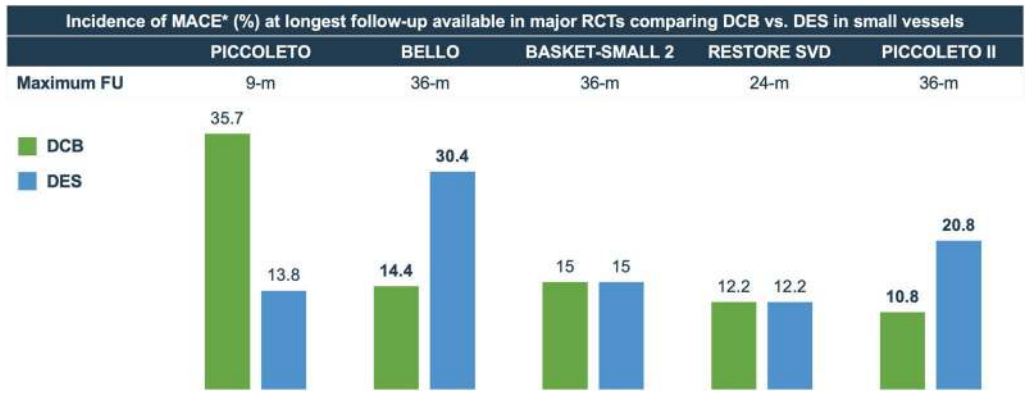


Fig. 26.3 Incidence of MACE in major RCT comparing DCB vs. DES in small vessels. Data from the longest follow-up available are reported for every single study. Differences in bold are statistically significant. FU follow-up, m months, MACE major adverse cardiac events, RCT randomized controlled trial, DCB drug-coated balloon, DES drug-eluting stent. MACE were defined as follows in each of the studies: PICCOLETO—All-cause death, new ST-segment elevation myocardial infarction, or target lesion revascularization; BELLO—All-cause death, myocardial infarction, or target vessel revascularization; BASKET-SMALL 2—Cardiac death, non-fatal myocardial infarction, or target vessel revascularization; RESTORE SVD—All-cause death, myocardial infarction, or repeat revascularization; PICCOLETO II—Cardiac death, myocardial infarction, or target lesion revascularization

as ≤2.75 mm). The efforts to accrue such evidence were prompted by the high risk of adverse events observed after small DES implantation [10, 11]. A total of five RCT have been conducted to compare outcomes of five different paclitaxel DCB vs. DES in small coronary vessels (Fig. 26.3) [11]. With the exception of one single RCT evaluating an early generation DCB within a cohort including an extremely low proportion of patients undergoing lesion preparation, all these studies demonstrated at least non-inferiority of DCB angioplasty vs. DES implantation in their primary endpoints [11], and the observed proportion of patients experiencing major adverse cardiac events at 3-year follow-up after DES implantation was up to 30%, double that among patients treated with DCB angioplasty [12, 13]. More recently, a promising level of observational data has been accruing for DCB angioplasty in long lesions irrespective of vessel size with the aim to avoid full-metal jacket, particularly in vessels densely populated by side branches such as the left anterior descending artery (Fig. 26.4), and data from RCT are underway (NCT04893291, NCT04859985) [14, 15].

As anticipated above, lesion preparation is also key in de novo disease. Routine predilation of crossable lesions via prolonged noncompliant balloon inflations with a 1:1 balloon-to-artery diameter ratio by angiography should aim for full balloon expansion in two orthogonal fluoroscopic views. In case of recoil, crossover to angioplasty with repeated, prolonged inflations at nominal pressure with specialty balloons such as scoring and cutting balloons, can follow. Conversely, in case of insufficient balloon expansion due to heavy calcification, noncompliant and specialty balloon inflation should be considered at high pressure [16]. Scoring or cutting balloon with a 1:1 balloon-to-artery diameter ratio on angiography can be inflated repeatedly to nominal pressure and for a prolonged time. In case of nondilatable segments, high-pressure noncompliant, scoring, or cutting balloon can be helpful but undersizing by 0.5 mm on angiography or 1 mm on intravascular imaging (media-to-media) is essential to prevent vessel perforation. Super non-compliant balloon inflation, intravascular lithotripsy and atherectomy should be considered when proof of sufficiently severe calcification is available or in resistant cases. Atherectomy remains the mainstay for device-uncrossable lesions.

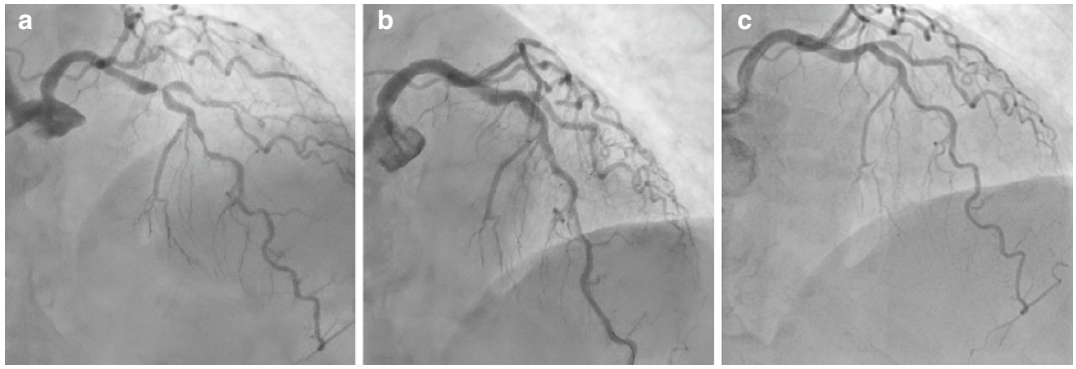


Fig. 26.4 DCB angioplasty for long lesions. (**a**) Long lesion involving a tortuous LAD in its proximal (in bifurcation with the first diagonal branch) and mid segments. (**b**) Lesion preparation, including cutting balloon inflation, was followed by DCB angioplasty with two balloons (3.0 × 40 mm and 2.0 × 40 mm). A linear dissection not compromising distal vessel flow was evident at angiography in the mid-LAD at the end of the procedure. (**c**) 6-month angiographic follow-up in an asymptomatic patient revealed no dissection and patent intervention site. DCB drug-coated balloon, LAD left anterior descending artery

26.6 Result Assessment After Lesion Preparation

Systematic evaluation of an adequate result in de novo disease, as in ISR, includes assessment for significant recoil or inadequate acute lumen gain (i.e., > 30% residual diameter stenosis). In addition, stability of the result is supported by absence of: chest pain, electrocardiogram ischemic changes, persistent contrast hang-up, progressive luminal narrowing, flow-limiting dissection and thrombolysis in myocardial infarction (TIMI) flow <3. To recognize a threatening dissection, when in doubt, a pressure wire can be adopted to evaluate the residual gradient across the dissected segment, although this strategy has not been validated in high numerosity prospective studies [17]. The role of intravascular imaging for routine assessment of dissections after lesion preparation is limited. Nonetheless, it is key to assess lumen gain in specific scenarios, such as ISR. It can also be useful to evaluate plaque and calcium burden in complex lesions and vessel size in diffuse disease.

26.7 DCB Angioplasty

DCB angioplasty with a 1:1 balloon-to-artery diameter ratio and a length ≥2 mm longer than the predilated segment at either end can be selected. Uneventful delivery of the last used (and often bulkiest) balloon can be used as indirect proof of sufficient support for DCB delivery. DCB delivery to the target lesion is time sensitive and should be performed in a pristine manner. Once positioned, it should be inflated to nominal pressure for 60–90 s to ensure appropriate drug delivery. At this point, result assessment should follow once again. Although no signs of inadequate or unstable result should be expected after DCB inflation at nominal pressure, PCI may proceed with additional lesion preparation and DCB angioplasty or stent implantation should any complication become evident.

26.8 Stenting

Stenting should be considered in presence of inadequate or unstable results, with the goal of covering the entire dissection if present and threatening (i.e., bailout stenting). While 5–15% of patients with de novo disease require bailout stenting [14, 17]. An up-front hybrid strategy including short stenting in the proximal segment and DCB angioplasty in the distal segment can also be considered when treating a long lesion [18].

26.9 Additional Emerging Indications for DCB Angioplasty

PCI involving bifurcation lesions represents about 20% of procedures, and can be particularly complex in terms of strategy selection, device requirement and delivery, simultaneous balloon inflations, overall procedure duration, and amount of contrast medium injected, especially in lesions requiring two-stent strategies. DCB not only allows simplification of the procedure, as most of the angioplasty can often be performed sequentially, but also allows positive vessel remodeling at locations where two-stent strategies would imply multiple stent layers (e.g. side branch ostium). DCB angioplasty can be implemented for treatment of the side branch in a provisional stenting strategy [19], of particular interest when treating the ostial left circumflex in distal left main bifurcation lesions. Angioplasty with a scoring or cutting balloon can be preferred for the preparation of ostial side branch lesions. Additionally, a DCB-only strategy can be considered after lesion preparation with an adequate and stable result. Sequential DCB delivery and inflation can usually follow (generally with the side branch first), while kissing DCB inflation could be planned in specific cases where carina shift is expected. Although evidence is accruing, high-numerosity prospective studies are currently lacking and eagerly awaited [20].

DCB angioplasty offers a promising approach for CTO by (i) minimizing extensive stenting, (ii) avoiding the possibility of stent undersizing, and (iii) allowing positive vessel remodeling. Both a DCB-only approach or a hybrid strategy combining DES implantation in the occluded segment and DCB angioplasty in the distal (often diffusely diseased) and negatively remodeled vessel could be advantageous.

A safe and effective metal-free strategy for treatment of coronary lesions in the setting of ACS is particularly appealing given the risk of implanting permanent struts within a vessel that may be larger than it appears in the context of an adrenergic surge. Results from studies evaluating DCB angioplasty for ACS are promising, though the amount of evidence is limited, especially in ST-segment elevation myocardial infarction [21]. Operators may consider thrombus aspiration before DCB inflation in presence of a thrombotic lesion, in order to optimize conditions for drug delivery onto the vessel wall. This approach in lesions may be discouraged in presence of high residual thrombotic burden. The recent DCB ARC Consensus document gives a clear snapshot of current DCB indications and implications [22].

26.10 Conclusion

DCB angioplasty represents an appealing strategy for delivering antiproliferative drug to the coronary vessel wall in the absence of a permanent foreign body. Although the first DCB was only recently approved in the United States purely for treatment of ISR, multiple scenarios within the PCI panorama could benefit from expanding DCB technologies, as suggested by results of clinical practice in other countries. A systematic approach with careful and judicious implementation of DCB angioplasty has the potential to further optimize the efficacy of PCI without jeopardizing patient safety.

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27 Drug-Coated Balloons and Antithrombotic Treatment

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27.1 The Potential Advantages of DCB Over DES in Terms of Antiplatelet Therapy Reduction (of Great Value in HBR Patients)

27.1.1 Drug-Eluting Stents and Antithrombotic Therapy

- Requires DAPT for at least 1 month, plus additional months depending on the context (ACS) or complexity of PCI (multiple stents, bifurcations-2 stents, very long stenting, etc).
- This requirement leads to a certain incidence of bleeding during follow-up, which is much higher in patients with HBR, representing around 40% of PCI patients [1, 2].
- Bleeding, especially major bleeding, reduces survival, both due to the event itself and due to the recurrence of MACE induced by discontinuation of DAPT [3].
- Discontinuation of DAPT in the first 30 days after DES implantation dramatically increases stent thrombosis. In the mid-term (1–3 months), discontinuation of DAPT/SAPT also increases the risk of thrombosis to a non-negligible extent; [4].

27.1.2 DCB and Antithrombotic Therapy

- Given the lack of a metallic cage, these are less dependent on DAPT and allow for shorter durations.
- In DES vs. DCB trials, a clear tendency for less bleeding with DCB is observed, despite similar or just slightly shorter DAPT durations [5, 6].
- In the event of bleeding, discontinuing DAPT is much safer, even in the first month.
- There have been positive experiences with the use of SAPT from the outset in cases of very-HBR [7–9].

27.2 The Antithrombotic Strategies Applied and Bleeding Outcomes in the DCB vs. DES Trials

The REC-CAGEFREE I was an open-label, randomised, non-inferiority trial conducted at 43 sites in China [10]. A total of 2272 patients were

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randomly assigned to the DCB group. Post-procedure care was similar to stenting. While a minimum of 30 days of DAPT was suggested, the actual DAPT duration was left to the discretion of the implanting physician and was similar between the groups, with many patients receiving DAPT for much longer, especially those with ACS. At the 3-year follow-up a lower Bleeding Academic Research Consortium (BARC) 3–5 bleeding rate was reported in the DCB group compared to the DES group (1.4% vs. 2.6%; $p = 0.05$).

The SELUTION trial, a randomized controlled trial (over 3300 patients), compared a sirolimus-eluting balloon strategy with provisional stenting to the standard treatment of systematic DES implantation for de novo coronary lesions [11]. Prior, during and after the index procedure, anti-platelet medication is given according to guidelines, and hospital practice. One-year results, presented in October 2025, demonstrated that the DEB strategy was non-inferior to the DES strategy, providing an effective alternative that avoids leaving a permanent implant. A significant interaction was found according to the HBR condition, with the DCB being particularly beneficial in the HBR subgroup.

In pooled analysis of trials, major bleeding is significantly lower with DCB angioplasty compared to DES, an effect mainly observed in trials adopting shorter DAPT durations for DCB [5, 6].

Therefore, in all trials, the DAPT strategies did not differ significantly between DCB and DES arms. These were just based on the medical criteria. However, as aforementioned, an overall lower bleeding risk was observed with DCB, which could be explained by a less stringent and somehow shorter DAPT regimes.

Table 27.1 presents the DCB vs DES RCTs conducted in de novo small vessel disease, describing the DAPT strategies and bleeding outcomes.

Table 27.2 presents the DCB vs DES RCT conducted in de novo large vessel disease, describing the DAPT strategies and bleeding outcomes.

Following Table 27.3 presents the DCB vs DES RCT conducted for in-stent restenosis lesions, describing the DAPT strategies and bleeding outcomes.

27.3 Randomized Trials Comparing Different Antithrombotic Regimes After DCB Therapy

Only one randomized trial has been published evaluating a stepwise dual antiplatelet therapy de-escalation in patients after drug-coated balloon angioplasty, the REC-CAGE FREE II [12].

Conducted in 41 hospitals in China, enrolled 1948 adults with acute coronary syndrome who received treatment exclusively with the Swine paclitaxel-coated balloons. Participants were randomly assigned (1:1) to either the stepwise DAPT de-escalation group ($n = 975$), consisting of aspirin plus ticagrelor for 1 month, followed by 5 months of ticagrelor monotherapy, and then 6 months of aspirin monotherapy, or to the standard DAPT group ($n = 973$), consisting of aspirin plus ticagrelor for 12 months. The primary endpoint was net adverse clinical events (all-cause death, stroke, myocardial infarction, revascularisation, and BARC type 3 or 5 bleeding) at 12 months in the intention-to-treat population. Non-inferiority was established if the upper limit of the one sided 95% confidence interval (CI) for the absolute risk difference was smaller than 3.2%.

Among all patients enrolled, 20.6% were at high bleeding risk. 60.9% of treated lesions were in small vessels, and 17.8% were for in-stent restenosis. At 12 months, the primary endpoint occurred in 87 (8.9%) participants in the stepwise de-escalation group and 84 (8.6%) in the standard group (P non-inferiority = 0.013). In the stepwise de-escalation versus standard groups, BARC type 3 or 5 bleeding occurred in 4 versus 16 participants (0.4% v 1.6%, $P = 0.008$), and all-cause death, stroke, myocardial infarction, and revascularisation occurred in 84 versus 74 participants (8.6% v 7.6%, $P = 0.396$). Treated as having hierarchical clinical importance by the win ratio method, more wins were noted with the stepwise de-escalation group (14.4% wins) compared with the standard group (10.1% wins) for the predefined hierarchical composite endpoint of all cause death, stroke, myocardial infarction, BARC type 3 bleeding, revascularisation, and BARC type 2 bleeding (win ratio 1.43 (95% CI

Table 27.1 Randomized controlled trials in de novo small vessel disease comparing drug-coated balloons vs. drug-eluting stent

Trial	Patients	Design	DAPT duration	Primary endpoint	Binary restenosis	TLR	Bleeding
PICCOLETO	57	DCB vs DES	1 month in CCS and DCB only 3 months in DCB + BMS 12 months in UA and DES	DS: 43.6% vs. 24.3%	32.1% vs 10.3%		Not included in primary or secondary endpoints. Not reported
BELLO	182	DCB vs DES	1 month in DCB only 3 months in DCB + BMS 12 months in DES	LLL: 0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm, difference (−0.21, 95% CI: −0.34 to −0.09; *p* noninferiority = <0.001; *p* superiority = 0.001)	8.9% vs 14.1%	4.4% vs 7.6%	Not included in primary or secondary endpoints. Not reported
RESTORE SVD	230	DCB vs DES	6 months in both groups	DS: 29.6 ± 2.0 vs. 24.1 ± 2.0, diference (5.5, 95% CI: 0.2–10.9; $p < 0.001$)	11.0% vs. 8.6%	4.4% vs. 2.6%	Not included in primary or secondary endpoints. Not reported
PICCOLETO II	232	DCB vs DES	1 month in CCS and DCB only 6 months in CCS and DES 12 months in ACS	LLL: 0.04 ± 0.28 mm vs. 0.17 ± 0.39&$$$;	6.3% vs 6.5%	5.6% vs 5.6%	0 BARC 3 to 5 bleedings reported in both groups
BASKET SMALL 2	758	DCB vs DES	1 month in CCS and DCB only 3 months in DCB + BMS 6 months in CCS and DES and DCB + DES 12 months in ACS	MACE at 12 months: 7.3% vs 7.5% (HR: 0.97; 95% CI: 0.58 to 1.64; $p = 0.92$)	3.4% vs. 4.5%	3.4% vs 4.5%	BARC 3–5 bleedings: (1.1% vs 2.4%; HR: 0.45 95% CI: 0.14–1.46)
PEPCAD NSTEMI	210 NSTEMI	DCB vs stent treatment (BMS/DES)	12 months in both groups	TLF: 3.8% vs 6.6% $p = 0.53$; difference −0.03, 97.5% CI: −0.105 to 0.05	Not reported	1% vs 1%	Not included in primary or secondary endpoints. Not reported

ACS acute coronary syndrome, *BARC* bleeding acording to the Academic Resarch Consortium, *BMS* bare-metal stent, *CCS* chronic coronary syndrome, *DAPT* dual antiplatelet therapy, *DCB* drug-coated balloon, *DES* drug-eluting stent, *DS* diameter stenosis, *LLL* late lumen loss, *MACE* mayor cardiovascular adverse events, *SVD* small vessel disease, *TLR* target lesion revascularization, *UA* unstable angina

Table 27.2 Randomized controlled trials in de Novo Large Vessel Disease comparing drug-coated balloons vs. drug-eluting stent

Trial	Patients	Design	DAPT duration	Primary endpoint	Binary restenosis	TLR	Bleeding
Nishiyama et al.	60	DCB vs DES	8 months in both groups	LLL: 0.25 ± 0.25 mm vs. 0.37 ± 0.40 m&$$$;	14.37 ± 8.2 vs 15.97 ± 15.87 $p = 0.63$	0.0% vs 6.1%	Not included in primary or secondary endpoints. Not reported
REVELATION	120 STEMI	DCB vs DES	12 months in both groups	FFR: 0.92 ± 0.05 vs. 0.91 ± 0.06 difference 0.12 (95% CI: 0.018 to 0.032; $p = 0.27$)	Not reported	3% vs 2%	BARC 3 or 5 bleeding: 0 in both groups
REC-CAGEFREE-I	2902 small vessel (55%)	DCB vs DES	Not specified. DCB group 6–12 months	DoCE: 6.4% vs 3.4% difference 3.04% upper boundary one sided 95% CI 4.52; p non inferiority = 0.65; two sided 95% CI 1.27 to 4.81; $p = 0.0008$	Not reported	3.1% vs 1.2%	1.4%) vs 27 (2.4%) difference −0.96%, (95% CI: −2.09 to 0.17, $p = 0.096$)
REC-CAGEFREE-II	1948 ACS small vessel (60.9%)	DCB only stepwise DAPT vs standard DAPT	1 month *T*, then 5 months *T*, then 6 months A: Stepwise DAPT 12 months: Standard DAPT	NACE: 8.9% vs 8.6% difference 0.36% upper boundary one sided 95% CI 2.47%; p non inferiority = 0.013	Not reported	3.8% vs 3.6%	BARC 3 or 5 bleeding: 4 (0.4%) vs 16 (1.6%) difference −1.19% (95% CI −2.07 to 0.31%. $p = 0.008$)
DEBUT	220 HBR ACS (96)	DCB vs BMS	1 month in both groups in both ACS and CCS	MACE: 1% vs. 14%	Not reported	0% vs 6%	BARC bleeding: 13% vs 10% $p = 0.59$
Yu et al	170	DCB vs DES	1–3 months in CCS and DCB 6–12 months in ACS and DCB 12 months if DES	LLL: −0.19 ± 0.49 mm vs 0.03 ± 0.64 upper boundary one sided 97.5% CI −0.04 mm p non inferiority = 0.019	28.5 vs 18 $p = <0.001$	1.2% vs 3.8%	Not included in primary or secondary endpoints. Not reported

A aspirin, *ACS* acute coronary syndrome, *BARC* bleeding acording to the Academic Resarch Consortium, *BMS* bare-metal stent, *CCS* chronic coronary syndrome, *DAPT* dual antiplatelet therapy, *DCB* drug-coated balloon, *DES* drug-elluting stent, *DS* diameter stenosis, *LLL* late lumen loss, *MACE* mayor cardiovascular adverse events, *NACE* net adverse clinical events, *SVD* small

Table 27.3 Randomized controlled trials in intra-stent restenosis disease comparing drug-coated ballons vs. drug-eluting stent

Trial	Patients, (*N*)	Design	DAPT duration	Primary endpoint	Binary restenosis	TLR	Bleeding
BMS-ISR							
PEPCAD II ISR	56	DCB vs PES	3 months in DCB vs 6 months in PES	LLL: 0.17 ± 0.42 mm vs 0.38 ± 0.61 mm; *P* value = 0.03	7% vs 20%	6.3% vs 15.4%	Not included in primary or secondary endpoints. Not reported
RIBS V	189	DCB vs EES	3 months in DCB vs 12 months in EES	MLD: 2.01 ± 0.6 mm vs 2.36 ± 0.6 mm; *P* value <0.001	9.5% vs 4.7%	6% vs 1%	Not included in primary or secondary endpoints. Not reported
TIS	136	DCB vs EES	3 months in DCB vs 6–12 months in EES	LLL: 0.09 ± 0.73 mm vs 0.44 ± 0.73 mm; *P* value = 0.0004	8.7% vs 19.12%	7.35% vs 16.18%	Not included in primary or secondary endpoints. Not reported
SEDUCE	50	DCB vs EES	NA	% of uncovered struts/ patient: 1.4% vs. 3.1%; *P* value = 0.025	26.4% vs. 11.4%	4.2% vs 8	Not included in primary or secondary endpoints. Not reported
DES-ISR							
Pepcad China ISR	220	DCB vs PES	12 months in both groups	LLL: 0.46 ± 0.51 mm vs 0.55 ± 0.61 mm; *p* for non-inferiority = 0.0005	18.6% vs 23.8%	15.6% vs 12.3%	Not included in primary or secondary endpoints. Not reported
RIBS IV	309	DCB vs EES	3 months in DCB vs 12 months in EES	MLD: 1.80 ± 0.6 mm vs 2.03 ± 0.7 mm; *P* value <0.01	19% vs 11%	13.0% vs 4.5%	Not included in primary or secondary endpoints. Not reported
Restore	172	DCB vs EES	6 months in both groups	LLL: 0.15 ± 0.49 mm vs 0.19 ± 0.41 mm; *P* value = 0.54	19.5% vs 5.6%	5.8% vs 1.2%	Bleeding events as one of the secondary outcomes: 18 (20.9%) vs 14 (16.3%); *P* value = 0.43
BMS-ISR/DES-ISR							
DARE	278	DCB vs EES	12 months in both groups	MLD: 1.71 ± 0.51 vs 1.74 ± 0.61; *P* for non inferiority <0.0001	18.1% vs 20.9%	8.8% vs 7.1%	Not included in primary or secondary endpoints. Not reported
Biolux	229	DCB vs SES	Given as per local standard	LLL: 0.03 ± 0.40 mm vs 0.20 ± 070; *P* value = 0.3984	NA	13.5% vs 11.6%	Not included in primary or secondary endpoints. Not reported

DCB drug-coated balloon, *EES* Everolimus-eluting stent, *LLL* late lumen loss, *MLD* minimal lumen diameter, *PES* paclitaxel-eluting stent, *SES* Sirolimus-eluting stent

1.12 to 1.83), $P = 0.004$). Results from the per-protocol and the intention-to-treat analysis were similar. The authors concluded that, among participants with acute coronary syndrome who could be treated by DCB exclusively, a stepwise DAPT de-escalation was non-inferior to 12 months DAPT for net adverse clinical events.

27.4 Results of DCB-Only Registries in Which SAPT Was Used

A study by B. Cortese and P. Serruys comprised a group of 107 patients treated with SAPT after DCB-only revascularization because of HBR or active bleeding. They analyzed the outcome of this cohort of patients at 1-year follow-up and compared it with the entire cohort of patients with DCBs [7].

Patients with SAPT had lower initial levels of hemoglobin and fewer acute coronary syndromes at presentation. At discharge, 35% of patients taking SAPT were treated with aspirin and 65% with clopidogrel for decision of the operator. The group treated with SAPT and the one treated with DAPT differed for several clinical and procedural characteristics, but procedural success and in-hospital outcome did not differ. After 1 year, the primary end-point of major adverse cardiac events (and its components cardiac death, myocardial infarction, target lesion revascularization) was not significantly different between the 2 groups (10% versus 9%, $P = 0.78$), but a reduction in the cumulative rate of 2 to 5 BARC bleedings was observed in the SAPT group (9% versus 6%, $P = 0.04$). After adjusting for confounding factors through multivariate analysis, bleeding diathesis, DAPT, and anticoagulant use were predictors of BARC bleedings, whereas bleeding diathesis and acute coronary syndromes were predictors of major adverse cardiac events. The authors concluded that the results of this study, while hypothesis-generating, might have important clinical implications.

In a study from Finland, 172 patients using the DCB-only strategy and discharged with SAPT were followed up [8]. The clinical presentation was CCS in 42% of the patients and ACS in 58%. The lesions treated were mainly de novo (96%). Most (87%) of the patients were at HBR with at least one major or two minor ARC risk factors for bleeding. Periprocedural DAPT was used in 49% of the patients. The 12-month major adverse cardiac events (composition of cardiovascular death, nonfatal myocardial infarction, and target-lesion revascularization) rate was 1.4% in stable CAD and 7.1% in ACS. The 12-month all-cause mortality after DBC only + SAPT strategy was 4.1% in stable CAD and 12.1% in ACS. The rate of ischemia-driven target lesion revascularization was 0% in stable CAD and 3.0% in ACS at 12 months. The 12-month rate of significant bleeding (BARC type 2–5) was 10.5%. There were no acute or subacute vessel closures. Despite the aged patient population with comorbidities, the TLR, MACE, and bleeding rates were low with DCB-only PCI combined with SAPT. The authors concluded that his novel approach could reduce the post-PCI bleeding risk in patients with CAD and HBR compared to stenting.

Finally, the most recent contribution in the field is a post hoc analysis of the All-comers Sirolimus-coated Balloon European Registry (EASTBOURNE) registry [9]. Among 2123 patients enrolled, 113 patients (5.8%) received SAPT while 1826 patients (94.1%) received DAPT. Most of the patients underwent DCB PCI for de novo lesions (56.3%) while 848 patients (47.7%) had DCB revascularization for in-stent restenosis. No cases of TLR occurred in the SAPT group within 1 month after the index procedure, and no acute occlusive events were recorded during follow-up in patients taking a single antiplatelet agent. Moreover, no differences in terms of TLR were observed between SAPT vs DAPT regimens. The cumulative rate of MACE at 12 months was not different between SAPT and DAPT regimens and results were consistent in the de novo and in-stent restenosis groups. Therefore, this post hoc analysis of the EASTBOURNE registry suggests that the use of single antiplatelet agent after sirolimus-DCB PCI for both de novo or in-stent restenosis lesions is safe and effective and can help to contain the risk of bleeding in a selected population.

In summary, these three studies, even though they are observational registries of limited size, yield consistent results suggesting that SAPT could be a safer alternative to DAPT in selected HBR patients undergoing DCB-only revascularization.

In this Table 27.4, these previously discussed registries are described in more detail.

Table 27.4 Results of DCB-only registries in which SAPT was used

	Cortese et al. [7]	Räsänen et al. [8]	Mangieri et al. [9]
Study design	Retrospective observational	Retrospective observational, single-center	Prospective, multicenter registry
Inclusion period	2012–2021	2011–2020	2016–2020
Patients on SAPT	107	172	113
Comparator group	Full DCB cohort (n = 1110)	None (SAPT only)	DAPT (n = 1826)
PCI strategy	DCB-based PCI	DCB-only PCI	DCB-only PCI
Mean/median age	71 (SAPT) vs 69 (DAPT); p = 0.71	75	67 (SAPT) vs 66 (DAPT); p = 0.33
Female sex	36% (SAPT) vs 39% (DAPT); p = 0.87	41%	24% (SAPT) vs 18% (DAPT)
Acute coronary syndrome	13% (SAPT) vs 45% (DAPT); p = 0.02	58%	35% (SAPT) vs 46% (DAPT)
Hemoglobin	9.9 g/dL (12 DAPT, p = 0.002)	12.3	12.7 (13.4 DAPT, p = 0.001)
High bleeding risk	100%	87% (≥1 major or ≥2 minor ARC-HBR criteria)	Not systematically assessed
Oral anticoagulation (%)	48% (SAPT) vs 27% (DAPT); p = 0.03	65%	Not reported
Antiplatelet agents	35% aspirin 65% clopidogrel	70% aspirin 22% clopidogrel 5% ticagrel 1% prasugrel	Not reported
De novo lesions (%)	100%	96%	56%
In-stent restenosis (%)	0%	4%	44%
Periprocedural DAPT	Not reported	49%	Not reported
Follow-up	12 months	12–24 months	12 months
MACE definition	Cardiac death, MI, TLR	Cardiovascular death, nonfatal MI, TLR	Overall death, MI, TLR
MACE at 12 months (%)	9% (SAPT) vs 10% (DAPT); p = 0.78	4.7% overall (1.4% stable CAD; 7.1% ACS)	11.2% (SAPT) vs 8.9% (DAPT); p = 0.4
Cardiac death at 12 months	2% (similar in both groups)	3% overall	No significant differences
BARC 2–5 bleeding at 12 months (%)	6% (SAPT) vs 9% (DAPT); p = 0.04	10.5%	Not detailed
BARC 3–5 bleeding at 12 months (%)	2% (similar in both groups)	2.3%	2.9% (SAPT) vs 0.6% (DAPT); p = 0.027
Vessel thrombosis/ abrupt vessel occlusion	0% (both groups)	0% (both groups)	0% (both groups)
Key message	Similar ischemic outcomes with reduced bleeding vs DAPT	Low TLR/MACE/bleeding rates in elderly, comorbid HBR patients	SAPT safe and effective, reduces bleeding risk in selected patients

ACS acute coronary syndrome, *CAD* coronary artery disease, *DAPT* dual antiplatelet therapy, *DCB* drug-coated balloon, *HBR* high bleeding risk, *ISR* in-stent restenosis, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *SAPT* single antiplatelet therapy, *TLR* target lesion revascularization

27.5 Recommendations Provided in the Published Consensus Documents on DCB and Finally

In the absence of enough evidence from trials evaluating different antiplatelet therapy strategies, the recommendations to be followed are just those provided by consensus documents from the most relevant associations.

A consensus of the Japanese Association of Cardiovascular Interventions and Therapeutics suggests 1–3 months DAPT in CCS patients (class IIa, level of evidence B) [13]. The possibility of a shorter DAPT cannot be ruled out given the absence of foreign materials in the coronary artery and the extremely low incidence of acute thrombotic occlusion reported in previous literature.

According to the second report of the Asia-Pacific Consensus Group, the possibility of discontinuing antiplatelet agents may arise sooner post-DCB treatment, particularly in cases of severe, life-threatening bleeding, than DES implantation [14]. Recent studies show no significant difference in thrombotic event rates between single antiplatelet agents after DCB and standard antiplatelet regimens, with lower major bleeding rates. These results suggest it could be a preferred option for this patient subgroup.

Finally, the DCB Academic Research Consortium project originated from the need to overcome the lack of standardization and comparability among studies on DCB [15, 16]. The DCB Academic Research Consortium represents a collaborative effort between academic research organizations and the most renowned interventional cardiology societies focusing on percutaneous coronary intervention in Europe, the United States, and Asia. In the document published in 2025, some recommendations are presented.

The DCB ARC recommends assessing patients deemed at HBR according to the ARC-HBR definitions [1]. According to the DEBUT trial, DCB-only PCI was found to be superior to BMS implantation in patients deemed at HBR in terms of MACE (1.9% vs 12.4%; $P = 0.003$ for superiority) at 9 months [17].

However, that trial did not investigate the optimal duration of DAPT. In a prespecified subgroup analysis of the BASKET-SMALL 2 trial addressing the HBR cohort, a trend toward reduced severe bleedings was seen after DCB-only PCI and a shorter duration of DAPT compared with DES and standard DAPT [18].

Although the use of current-generation DES allows short 1-month DAPT [19], the optimal composition and duration of antiplatelet therapy after DCB-only PCI have not yet been established. The current consensus on DAPT duration after DCB-only PCI in patients with chronic coronary syndrome is 1 month, stemming from the first RCT of DCBs for the treatment of ISR [20], with this duration then adopted for the treatment of all de novo lesions.

Because of the lack of a metallic foreign body, the use of DCBs could offer advantages for patients at HBR, including shortening DAPT to <1 month or, in case of life-threatening bleeding, the possibility of stopping antiplatelet therapy during the first month. Recent registry studies suggest that DCB-only PCI can be safely done using a single antiplatelet agent in selected populations [7–9].

Said all this, outstanding questions remain regarding optimal antiplatelet regimens in DCB-only treated patients.

27.6 Our Own Recommendations Based on All Reviewed Data

Our proposal for antiplatelet therapy in DCB-only treated patients comes from a personal interpretation of all the reviewed data, acknowledging the lack of clinical evidence from randomize trials (Fig. 27.1).

The first consideration is the condition of the patient with respect to the bleeding risk, with three categories, no-HBR, HBR, and extreme HBR. Then, the clinical presentation, CCS vs ACS.

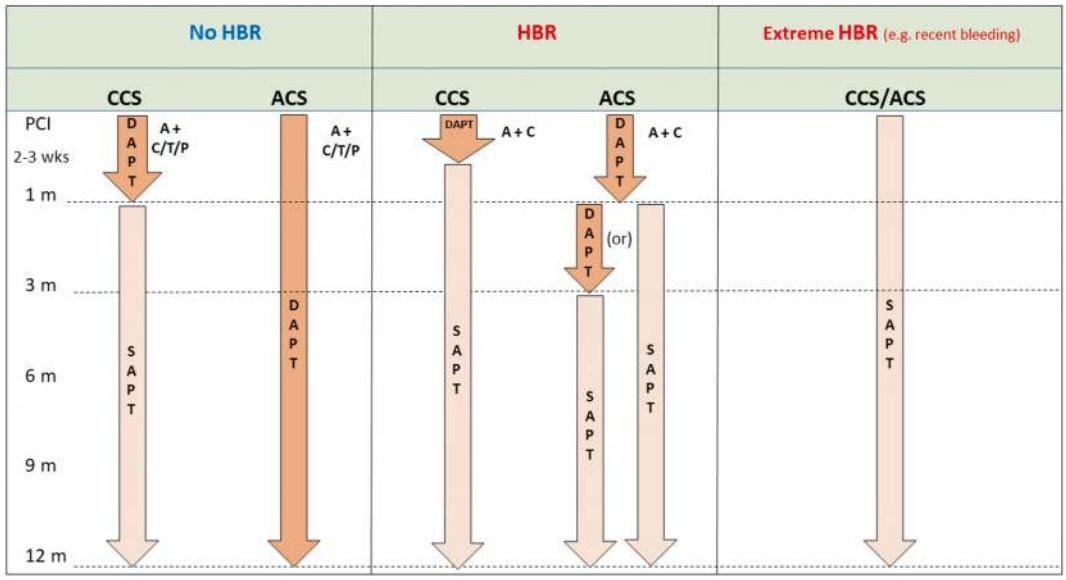


Fig. 27.1 Antiplatelet therapy in DCB-only treated patients during the first year. DAPT dual antiplatelet therapy, SAPT single antiplatelet therapy, A Aspirin, C Clopidogrel, T Ticagrelor, P Prasugrel

The risk of bleeding is not dichotomic or binary, is a continuum, and admits at least three categories. In this line, the PRECISE-HBR score stratifies bleeding risk and categorize patients as very high bleeding risk (1-year BARC 3 or 5 bleeding rate: ≥6% [score ≥27]), high bleeding risk (1-year rate: ≥4% and <6% [score 23–26]), and non-high bleeding risk (1-year rate: <4% [score ≤22]) [21].

In the no-HBR patients, the time for DAPT in CCS is 1 month, and after ACS is 12 months. DAPT could be implemented with any of the oral P2Y12 inhibitors [22–26].

In the HBR population, the patients with CCS could be treated for 2–3 weeks with DAPT and then with SAPT, whereas those after ACS could receive 1–3 months of DAPT depending on the individual features. DAPT should be implemented with Clopidogrel.

The complex group of patients showing a very high or an extreme HBR could be treated just with SAPT from discharge.

27.7 Ongoing Trials That Will Shed Light on the Field

Drug-Coated Balloon in Anticoagulated and Bleeding Risk Patients Undergoing PCI (DEBATE), NCT04814212. The purpose of this study is to compare DCB with DES in stable CAD or ACS patients who are at high risk of bleeding. The hypothesis of the DEBATE trial is that the strategy using DCB and a shorter DAPT regimen is non-inferior to the treatment using DES and longer DAPT duration in patients with high bleeding risk. If non-inferiority is shown, the superiority of the DCB strategy over the DES strategy will be tested.

Drug-Coated Balloon in Patients With High Bleeding Risk (DCB-HBR). NCT05221931. This is a prospective, multi-center, open-label, randomized controlled, noninferiority trial. The aim of the study is to compare clinical outcomes of DCB with DES for the treatment of de-novo coronary lesions in patients with HBR.

PICCOLETO IV (EU-CT: 2024-519706-13-0) is an international randomized clinical trial and is designed to test the hypothesis that a SAPT is not inferior to DAPT in patients at HBR or >75 years who have undergone solo-DCB angioplasty. The study will compare the effectiveness and safety of these two antiplatelet treatments to determine the best course of action for patients. This trial, led by Fondazione RIC, is run in collaboration with Fundacion EPIC in Spain.

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28 Reimbursement Policies and Cost-Effectiveness of Drug-Coated Balloons

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28.1 Introduction

Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) remains the standard of care for treatment of coronary artery disease and is endorsed by international clinical practice guidelines [1]. Despite their proven efficacy, DES are associated with long-term limitations related to the presence of a metallic scaffold, including a persistent annual risk of stent failure of about 2–3% driven by mechanisms such as restenosis, late thrombosis, and neoatherosclerosis [2–4]. These risks accumulate over time and are of particular relevance in patients with long life expectancy or complex coronary anatomy.

Drug-coated balloons (DCB) have emerged as an alternative revascularization strategy in selected clinical settings, most notably in the treatment of in-stent restenosis (ISR) and in patients at high bleeding risk [5, 6]. In addition, growing evidence supports the use of DCB in other lesion subsets, including coronary bifurcations and de novo disease in small vessels [7]. Unlike DES, DCB delivers an antiproliferative drug directly to the vessel wall without leaving a permanent implant, preserving native vessel anatomy, facilitating vascular healing, and reducing the substate for chronic inflammation and late adverse events [8, 9].

An important clinical implication of a "leave-nothing-behind" strategy is the potential to shorten the duration of dual antiplatelet therapy (DAPT). Prolonged DAPT is often required following DES implantation and is associated with an increased risk of bleeding, particularly in elderly patients or those with a history of hemorrhagic events [10, 11]. By minimizing or avoiding permanent scaffolding, DCB-based PCI may offer both safety and quality-of-life advantages in appropriately selected patients.

Beyond clinical considerations, the adoption of DCB technology is strongly influenced by cost and reimbursement frameworks. Although DCB may carry higher upfront device costs compared with conventional balloons or some DES platforms, economic analyses from the United States, Europe, and Asia suggest that reduced rates of repeat revascularization, shorter DAPT duration, and lower bleeding-related expenditures may off-

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set initial expenses over time. Clear and evidence-aligned reimbursement policies are therefore essential to support the appropriate use of DCB, ensure equitable patient access, and promote efficient allocation of healthcare resources. This chapter reviews current reimbursement models and cost-effectiveness data for DCB, highlighting challenges and opportunities for wider implementation in contemporary PCI practice.

28.2 Cost-Effectiveness of Drug-Coated Balloons

28.2.1 United States

Economic evaluations from the United States have examined the cost-effectiveness of drug-coated balloons across several vascular territories, primarily from the perspective of healthcare payers. In femoropopliteal artery disease, a U.S.-based analysis compared DCB angioplasty with standard percutaneous transluminal angioplasty (PTA) over a 2-year time horizon. Although DCB angioplasty incurred higher initial procedural costs, exceeding standard PTA by $1129 per patient, largely attributable to device pricing, this was offset by lower downstream costs. Target limb–related expenditures between discharge and 24 months were $1212 lower in the DCB group, resulting in comparable total discounted costs at 2 years ($11,277 for DCB vs. $11,359 for PTA; $p = 0.97$). Patients treated with DCB demonstrated a numerical, though not statistically significant, increase in quality-adjusted life years (QALYs) (1.53 ± 0.44 vs. 1.47 ± 0.42; $p = 0.40$). Probabilistic cost-effectiveness analyses indicated a 70% likelihood of DCB angioplasty being cost-effective at a willingness-to-pay threshold of $50,000 per QALY, increasing to 79% at $150,000 per QALY [12].

Cost-effectiveness has also been evaluated for DCB use in arteriovenous fistula (AVF) stenosis. A Markov model comparing DCB with plain old balloon angioplasty (POBA) over 2 years found that POBA produced marginally better quality-of-life outcomes but at a higher overall cost, yielding an incremental cost-effectiveness ratio (ICER) of $27,413 per QALY and favoring POBA in the base-case analysis. Sensitivity analyses demonstrated that DCB became cost-effective if the 2-year mortality rate following DCB treatment was no more than 3.4% higher than that of POBA. When equal mortality was assumed, DCB remained cost-effective provided the incremental procedural cost did not exceed $4213 [13]. These findings underscore the importance of long-term outcomes and procedural pricing in determining value-based reimbursement.

28.2.2 Europe

European cost-effectiveness analyses of DCB are supported by a robust body of evidence, reflecting diverse healthcare systems with centralized reimbursement models. A UK-based pooled analysis combined data from 28 studies involving 5167 femoropopliteal lesions to compare drug-eluting endovascular strategies, including DCB, DES, and bare-metal stents (BMS). Over 24 months, target lesion revascularization (TLR) rates were reduced from 36.2% to 17.6% with DCB, 19.4% with DES, and 26.9% with BMS. Incremental per-patient costs were modest (£43 for DCB, £44 for DES, and £112 for BMS), with DCB demonstrating the most favorable cost-effectiveness profile (ICER £3983 per QALY gained), compared with DES (£4534) and BMS (£20,719). A 10% reduction in device price rendered both DCB and DES strategies cost-dominant [14].

From a German healthcare payer perspective, a Markov state-transition model compared DCB angioplasty with POBA and repeat DES implantation. Although initial procedural costs were higher for DCB (€3488 vs. €2782 for POBA), DCB angioplasty was associated with lower total costs at 6 months (€4028 vs. €4169) and greater effectiveness in life-years gained (0.497 vs. 0.489). Repeat DES implantation was associated with intermediate costs and effectiveness. Key drivers of cost-effectiveness included TLR rates,

procedural costs, and duration of dual antiplatelet therapy (DAPT) [15].

In peripheral arterial disease, particularly femoropopliteal lesions, paclitaxel-coated balloons have been extensively evaluated. Analyses from the Netherlands and Germany demonstrated that urea excipient–based DCB in patients with chronic limb-threatening ischemia resulted in improved QALYs and overall cost savings at 24 months, approximately €1030 per patient in the Netherlands and €513 in Germany. These savings were primarily driven by reductions in repeat interventions and restenosis [16].

Economic evaluations in coronary artery disease have similarly suggested potential value for DCB strategies. In de novo coronary lesions, European studies comparing DCB with DES reported slightly higher per-patient costs for DCB (£3153.00 vs. £3143.98), but lower costs on a per-lesion basis (£3007.56 vs. £3051.85). Probabilistic sensitivity analyses showed a 92.3% probability of DCB being cost-saving per lesion. These findings suggest that a DCB-only approach may offer economic advantages in selected coronary lesion subsets [17].

In a small German coronary artery disease study, DCB treatment was associated with marginally lower rates of major adverse cardiovascular events compared with DES (14.5% vs. 15.3%), slightly lower quality-adjusted life expectancy over 3 years (2.35 vs. 2.36 QALYs), and lower direct medical costs (€5243 vs. €5341). The ICER for DES relative to DCB was €6863 per QALY gained, while DCB was both less costly and more effective in preventing major adverse cardiovascular events [18].

Cost-effectiveness has also been demonstrated for DCB use in coronary in-stent restenosis (ISR). Despite higher upfront procedural costs compared with repeat DES implantation or POBA, DCB therapy has been associated with lower overall costs and greater life-years gained, supporting its economic and clinical value in European healthcare systems [19].

28.2.3 Asia

In Asia, economic evaluations of DCB have focused largely on arteriovenous access and peripheral vascular disease. Decision-analytic models based on data from the IN. PACT AV Access trial demonstrated that DCB therapy reduced the number of reinterventions and associated costs in patients with AVF stenosis. In Korea, cost savings were observed at both three and 5 years, whereas in Japan, cost savings became evident after 5 years, reflecting differences in healthcare utilization and reimbursement structures [20].

In Singapore, a Markov model compared DCB with conventional balloon angioplasty for patients with AVF and arteriovenous graft (AVG) dysfunction. At a 3-year time horizon, DCB therapy was not cost-effective (net monetary benefit [NMB] = –S$1424), but it was cost-effective at 1 year (NMB = S$356) and 6 years (NMB = S$3738). The probability of cost-effectiveness increased from 34.5% at 3 years to 58.6% and 59.9% at 1 and 6 years, respectively. Although DCB use was associated with fewer AVF/AVG abandonments, this difference did not reach statistical significance ($p = 0.21$), and no significant differences were observed in other modelled outcomes [21].

Overall, economic evidence from Europe and Asia supports the cost-effectiveness of DCB across peripheral arterial disease, coronary de novo lesions, and in-stent restenosis (Table 28.1). While upfront device costs remain a barrier in some healthcare systems, reductions in repeat revascularization, DAPT-related complications, and long-term resource utilization suggest meaningful economic value. National reimbursement policies that align with this evidence may facili-

Table 28.1 Studies assessing DCB cost-effectiveness

Study & year/ country	Method	Comparison	Population	Findings
Salisbury et al. (2016) [12]/ USA	Cost-effectiveness was evaluated as cost per quality-adjusted life-year gained using a decision-analytic framework based on trial-derived data, assuming equal long-term mortality between treatment groups.	DCB Versus PTA	Femoropopliteal artery disease	DCB had higher initial cost (+$1129/patient) but lower follow-up costs (−$1212). Total 2-year costs were similar ($11,277 vs $11,359; $p = 0.97$). QALYs favored DCB (1.53 vs 1.47). Probability of cost-effectiveness was 70% at $50,000 per QALY gained and 79% at a threshold of $150,000 per QALY gained.
Zhou et al. (2016) [13]/ USA	A Markov model over 2-year time. Costs were estimated using Medicare reimbursement rates and published cost data, adjusted to 2021 values. Health outcomes were expressed as quality-adjusted life years, with sensitivity analyses conducted using a willingness-to-pay threshold of $100,000 per QALY.	DCB versus POBA	Arteriovenous Fistula Stenosis	POBA yielded slightly higher QALYs but at greater cost, with an ICER of $27,413/QALY. DCB became cost-effective if 2-year mortality was ≤3.4% higher than POBA or if added DCB cost per procedure was ≤$4213.
Katsanos et al. (2016) [14]/ UK	A decision-analytic model was applied over a 2-year horizon, incorporating the index procedure and up to one reintervention. Cost inputs were derived from the 2015/2016 NHS England Tariff (Enhanced Tariff Option) and Hospital Episodes Statistics data.	Drug-eluting endovascular treatment strategies compared with standard of care.	Femoro-popliteal artery disease.	TLR reduced from 36.2% to 17.6% (DCB) vs 19.4% (DES) and 26.9% (BMS). Incremental costs were £43 (DCB), £44 (DES), £112 (BMS). ICERs were £3983/QALY (DCB), £4534/QALY (DES), and £20,719/QALY (BMS).
Dorenkamp et al. (2013) [15]/Germany	A Markov state-transition model was used, with input parameters derived from the literature, and costs evaluated from the German healthcare payer perspective over a 6-month horizon.	DCB versus POBA versus DES	Drug-eluting stent restenosis.	Total costs were €4028 (DCB), €4169 (POBA), and €4101 (DES) over 6 months. LYs gained were 0.497 (DCB), 0.489 (POBA), and 0.494 (DES). DCB was both least costly and most effective.
Pietzsch et al. (2022) [16]/ Netherlands and Germany	A decision-analytic Markov model was applied with a 2-year time horizon, estimating strategy-specific quality-adjusted life-year gains based on survival and health state–specific utility values. A willingness-to-pay threshold of €50,000 per QALY was assumed.	Urea excipient-based DCB versus standard-of-care	Femoropopliteal peripheral artery disease	DCB reduced TLR (26.2% vs 32.8%) and amputations (2.8% vs 11.9%). QALYs increased by 0.017. Net savings were €1030 (Netherlands) and €513 (Germany), making DCB cost-saving.

(continued)

Table 28.1 (continued)

Study & year/ country	Method	Comparison	Population	Findings
Merinopoulos et al. (2023) [17]/UK	A cost-minimization analysis was performed comparing the total costs of patients treated with DCB or DES for first presentation of STEMI, NSTEMI, or stable angina due to de novo coronary artery disease.	DCB versus second generation DES.	De novo coronary artery disease	Per-patient cost slightly higher with DCB (£3153.00 vs £3143.98), but per-lesion cost was lower (£3007.56 vs £3023.07), supporting economic equivalence with potential lesion-level savings.
Cattaneo et al. (2025) [18]/ Germany	A cost-effectiveness analysis was conducted using German diagnosis-related group data to estimate total expected costs and quality-adjusted life expectancy, expressed in QALYs.	DCB versus DES	Small vessel coronary artery disease	During the 3 years follow-up direct costs were lower with DCB (€5243 vs €5341). QALYs were similar (2.35 vs 2.36). ICER for DES vs DCB was €6863/QALY; DCB reduced MACE at lower cost.
Bonaventura et al. (2012) [19]/Germany	A Markov state-transition decision-analytic model was used, with costs evaluated from the healthcare payer perspective and effectiveness expressed in life-years gained.	Paclitaxel-eluting stent versus paclitaxel-coated balloon angioplasty	Coronary Bare Metal Stent (BMS) In-stent restenosis (ISR)	Over 1 year time, total costs were lower with DCB (€4130.38 vs €5305.30). Life-years gained favored DCB (0.983 vs 0.976 years), over DES.
Lau et al. (2022) [21]/ Singapore	A Markov model–based economic evaluation was conducted, with effectiveness measured in quality-adjusted life years (QALYs). Cost-effectiveness was assessed using incremental net monetary benefit (NMB) at a Singapore willingness-to-pay threshold of S$87,000.	DCB versus PTA	Arteriovenous fistulas and arteriovenous grafts	DCB showed positive NMB at 1 year (S$356) and 6 years (S$3738), but not at 3 years (–S$1424). Probability of cost-effectiveness was 58.6% at 1 year and 59.9% at 6-years, whereas 34.5% at 3 years
Chun et al. (2022) [20]/ Korea and Japan	A decision-analytic model was developed to calculate strategy-specific costs for Korea and Japan over 5-year follow-up.	DCB versus PTA	Arteriovenous fistula stenosis	At 3 and 5 years, DCB therapy was associated with cost savings of ₩1,394,451 and ₩2,358,904, respectively, compared with percutaneous transluminal angioplasty in Korea, while corresponding savings in Japan were ¥34,337 and ¥149,701.

POBA plain old balloon angioplasty, *DCB* Drug-coated balloon, *DES* drug-eluting stent, *QALY, ICERs, NHS* National Health Service, *TLR* target lesion revascularization, *Lys* life-years, *ICER* Incremental Cost-Effectiveness Ratio, *QALY* Quality-Adjusted Life Year, *NMB* net monetary benefit, *PTA* percutaneous transluminal angioplasty

tate appropriate adoption of DCB, improve patient outcomes, and contribute to sustainable healthcare expenditure.

28.3 Reimbursement Policies

Reimbursement for DCB has evolved in parallel with the accumulation of clinical and economic evidence supporting its use. In the coronary space, the AGENT DCB is currently indicated for the treatment of coronary in-stent restenosis (ISR) in the United States. The AGENT IDE trial demonstrated a significant reduction in target lesion failure at 1 year, decreasing from 28.7% with conventional balloon angioplasty to 17.9% with AGENT DCB therapy. In addition, treatment with AGENT DCB was associated with lower rates of stent thrombosis, target lesion revascularization, and target vessel myocardial infarction, providing a strong clinical rationale for payer recognition of this technology [22].

In the United States, reimbursement pathways for AGENT DCB were substantially strengthened in 2025 when the Centers for Medicare and Medicaid Services (CMS) granted New Technology Add-On Payments (NTAPs), acknowledging the incremental costs associated with DCB use in both inpatient and outpatient prospective payment systems. In the outpatient setting, Transitional Pass-Through (TPT) payments further support facility reimbursement by allowing additional payment for the DCB device itself, potentially covering the full device cost when appropriately coded (e.g., HCPCS code C9610). To facilitate accurate procedural reporting, the American Medical Association (AMA) introduced Category III Current Procedural Terminology (CPT) codes 0913T and +0914T, effective January 2025. These codes are expected to transition to Category I status as clinical adoption and evidence continue to expand [23–25]. By 2026, the only DCB approved for CAD (specifically, ISR) in the USA will remain the Agent balloon. Other devices have started the FDA IDE approval process: Selution (Cordis, USA), Prevail (Medtronic, USA), and Magic Touch (Concept Medical, USA) have the potential for reaching the approval before 2028, if the results of the clinical trials they are involved in will lead to a green light by the regulatory authority.

In the United Kingdom, reimbursement for DCB use, particularly in peripheral arterial interventions, is incorporated into the National Health Service (NHS) payment framework through a combination of diagnosis-related group (DRG)–based tariffs and device-specific add-on payments, rather than relying solely on a flat angioplasty tariff. Similar approaches have been adopted in other European systems, including England and Germany, where specific DRG adjustments or add-on mechanisms recognize the higher acquisition cost of DCB devices used in lower extremity angioplasty [26]. Importantly, cost-effectiveness analyses conducted within the UK NHS context have demonstrated that DCB provides meaningful clinical benefits at acceptable incremental costs per QALY gained in femoropopliteal disease, supporting continued reimbursement under current models [14].

France represents a notable example of formal health technology assessment–driven reimbursement. Following positive evaluation, the first peripheral DCB (IN.PACT Admiral, Medtronic) was approved for add-on reimbursement and listed on the national reimbursement schedule (Liste des Produits et Prestations Remboursables, LPPR) through a ministerial decree. This decision enabled separate payment for the device in addition to standard procedural tariffs, facilitating broader clinical uptake [27, 28]. Similarly, in Germany and several Nordic countries, reimbursement systems account for the use of drug-eluting technologies, including DCB, through supplementary payment codes or higher procedure-based reimbursements compared with standard balloon angioplasty [29].

Across healthcare systems, coverage and reimbursement decisions are increasingly guided by formal assessments of both clinical effectiveness and cost-effectiveness [30]. Collectively, recent policy updates in the United States, the United Kingdom, and continental Europe reflect growing recognition of the value of DCB in coronary and peripheral interventions. As evidence

continues to expand into new clinical indications, alignment between reimbursement frameworks and real-world clinical value will be critical to ensuring equitable patient access and sustainable adoption of DCB technology [31–33].

28.4 Conclusion

DCB is now established as an effective revascularization strategy for both coronary and peripheral vascular disease. Although the upfront acquisition cost of DCB is higher than that of conventional balloon angioplasty and, in some settings, drug-eluting stents, accumulating evidence from the United States, Europe, and Asia demonstrates that these initial expenditures are frequently offset over time. The economic value of DCB therapy is driven by reductions in repeat revascularization, sustained vessel patency, avoidance of permanent implants, and favorable quality-adjusted life outcomes.

Cost advantages are most consistently observed in clinical scenarios characterized by high rates of restenosis and repeat interventions, including coronary in-stent restenosis, femoropopliteal artery disease, arteriovenous fistula dysfunction, and selected de novo coronary lesions. In these settings, the cumulative costs of recurrent procedures, prolonged dual antiplatelet therapy, and complication-related hospitalizations can substantially exceed the initial device cost, making DCB-based strategies economically attractive.

Reimbursement frameworks in many healthcare systems have evolved in response to this growing body of clinical and economic evidence. In regions such as the United States and Europe, the introduction of dedicated billing codes, add-on payments, and device-specific reimbursement pathways has helped to mitigate the impact of higher upfront costs and facilitate appropriate clinical adoption. When used in well-selected lesions and supported by reimbursement policies aligned with demonstrated value, DCB offers a revascularization approach that is both clinically effective and economically sustainable.

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29 Current Technical Challenges and Future Directions of Drug-Coated Balloons

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29.1 Introduction

Balloon angioplasty is currently considered a complement to coronary stenting and it is frequently used to prepare atherosclerotic plaques for subsequent stenting deployment or to optimize stenting results. Indeed, standalone balloon angioplasty has several limitations, such as vessel dissection, elastic recoil, constrictive remodeling, and intimal hyperplasia. Acute vessel closure may occur in up to 5% of patients as a result of an occlusive dissection with or without thrombus, while restenosis after percutaneous coronary angioplasty is between 30% and 60% in the first month [1–3]. DCB can overcome the intimal hyperplasia and the smooth cells migration, preventing long-term restenosis, but the intrinsic limitations of balloon angioplasty still remain with this technology. The lack of scaffolding and mechanical support allows its application especially in peripheral arteries, where DCB is more commonly used, or in specific coronary settings where the available stenting technologies failed to obtain optimal results.

Currently, in-stent restenosis (ISR) and small vessel disease are the main, but not the only ones, settings where DCB showed safe and effective outcomes [4]. In this chapter, we go through the current challenges for DCB technologies, and try to delineate the future directions for this technology.

29.2 DCB and Peripheral Atherosclerosis

29.2.1 Severe Calcifications and High Plaque Burden

Arterial atherectomy + DCB has shown a reduced need for bailout stenting vs. DCB alone in the superficial femoral artery setting [5]. Severe calcification and high plaque burden have been demonstrated to be independent predictors for late lumen loss (LLL) and target lesion revascularization (TLR), and are associated with a higher risk of procedural complications such as dissection [6]. Furthermore, vascular calcification, through a variety of mechanisms, presents a potential hindrance to the delivery and absorption of paclitaxel or sirolimus when delivered by

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DCB. Dense intimal calcification may promote the washoff of the drug, while medial calcinosis may prevent adequate drug penetration into the adventitia, recoil, and dissection.

A variety of atherectomy techniques allow for debulking of calcified, exophytic plaque prior to angioplasty or stenting [7]. Drug elution and its retention into the vessel wall are the mainstay on which the DCB technology is based. Heavily calcific plaques are the most important barrier to proper delivery, resulting in poor outcomes and hindering DCB efficacy. This theoretical concept has been demonstrated in several studies showing how calcific segments (in particular, the circumferential extent of calcification over their length) have a worse primary patency than non-calcific plaques [6, 8].

In this setting, the combination of debulking followed by DCB technology to achieve the best outcome for both acute and long-term success seems an attractive approach for these patients.

Several, single-center studies combining directional atherectomy (DA) and DCB have tried this approach for patients with lower limb arterial disease. These reports, most of which consisted of small samples, showed promising results from the combination of these two techniques.

In one study, the combination of DA and DCB (n = 60) was compared with DA with non-DCB angioplasty (n = 29). The primary patency was 84.7% in the DCB group compared with 43.8% in the non-DCB group [9]. Another single-center experience showed that the combination of DCB and DA provided a 90% freedom from clinically driven TLR in 30 patients with heavily calcified lesions [10]. Thus, the combination of DA with the added technology of DCB seems to be an attractive approach in patients with significant arterial obstructive disease. Clearly, scientific data are still scarce, and the cost-benefit analysis of this approach deserves further evaluation. Actually, the only randomized, multicenter, pilot feasibility study accomplished in this setting is the DEFINITIVE AR study (T. Zeller, "unpublished data", November 2014). This study was designed to assess and estimate the effect of treating vessels with DA prior to a DCB randomizing 1:1 claudicant patients with 7- to 15-cm SFA and/or popliteal lesions to either DA + DCB or to DCB alone. Subjects with severely calcified lesions were assigned to a nonrandomized registry arm and were treated with DA + DCB. One hundred twenty-one subjects were enrolled, 48 in the DA + DCB arm, 54 in the DCB arm, and 19 in the severely calcified lesion DA + DCB registry group. Mean lesion length ranged from 9.7 to 11.9 cm. In the randomized groups, the primary endpoint, percent stenosis at 12 months, was similar in both cohorts. Angiographic patency (≤50% stenosis and without TLR) was 82.4% in the DA + DCB arm and 71.8% in the DCB arm. The major adverse event rate, defined as a composite of clinically driven TLR, death, and major amputation, was 11.6% for the randomized DA + DCB arm, 9.8% for the randomized DCB arm, and 5.9% for the severely calcified lesion registry arm. This pilot study suggests an added benefit for combination therapy (DA + DCB) in long and calcified lesions that was not observed in the DCB-alone subgroup. Further investigation in larger, prospective, statistically powered randomized trials is warranted. While more recent studies of self-expanding nitinol stents and drug-eluting stents have demonstrated improved patency compared to bare metal stents, restenosis rates still approach 20–40% at 12 months [5]. Furthermore, stent fractures have been shown to occur in up to 37% of cases and markedly increase the risk of associated restenosis and occlusion [11]. Finally, the presence of a permanent vascular implant such as a stent may limit options for future surgical or endovascular therapies, should they be necessary. As a result, technologies and techniques that reduce bailout stenting may lead to more desirable outcomes in patients with FP disease.

29.3 DCB and Coronary Atherosclerosis

29.3.1 Severe Calcifications

In the coronary setting, due to the possible suboptimal expansion of DES implanted in heavily

calcified coronary lesions, several pilot studies evaluated the comparison of DES and DCB following atherectomy in this scenario.

One angiographic study evaluated the LLL of calcific coronary lesions at 13 months of angiographic FU. At this time point, the frequency of binary restenosis was 21.1%, and late lumen loss was 0.34 ± 0.30 mm [12]. Moreover, two randomized studies compared DCB vs DES in a calcific coronary setting.

In one study DCB (SeQuentPlease PEB, B. Braun, Berlin, Germany) was non-inferior to DES in terms of TLR, TVR (Target vessel revascularization), and MACE (Major adverse cardiovascular events) [13]. In a more recent randomized comparison of DCB (SeQuentPlease PEB, B. Braun, Berlin, Germany) vs DES following OA, the results showed non-inferiority in terms of MACE and, more interestingly, a lower rate of late lumen loss at 1 year OCT FU in the DCB group [14].

Calcific lesions have always been considered the biggest limitation for the application of DCB [15–18]. Calcium was deemed a natural barrier to the single-dose drug application diffusion into the vessel wall. The studies investigating this setting are showing that an adequate vessel preparation allows good results even in the most complex clinical setting, irrespective of the location (i.e. coronary or peripheral). Based on these results, DCB represents a valuable device in the interventionalist's toolkit when specific clinical and atherosclerotic settings (highly calcific lesions, high bleeding risk patients) display relative contraindication to DES implantation. More evidence is needed to understand the ideal context for the use of DCBs and, above all, the differences between the various devices currently available on the market are yet to be determined.

29.3.1.1 Future Directions for Severely Calcific Lesions

More recently, the investigator-driven CARDIAC study preliminary results (Fondazione Ricerca e Innovazione Cardiovascolare, D Benedetto, B Cortese et al., TCT 2025, unpublished data) showed the safety and efficacy of a solo-DCB approach in 121 patients with severe coronary calcifications undergone rotational, orbital atherectomy or intravascular lythotripsy. All patient lesions have been assessed by an independent core laboratory. The procedural success rate (by angiographic results <30% residual diameter stenosis and TIMI 3 flow) was 100%, with no major complications such as vessel perforation. At a median follow-up of 384 days (IQR 185–453), target lesion failure (TLF) occurred in 8 patients (6.6%). Final results will be presented in 2026.

The role of less invasive tools like scoring or cutting balloons prior to DCB angioplasty in severely calcified lesions is being addressed by the ongoing PICCOLETO XI study Cohort A (ISR) and Cohort B (de novo lesions) (NCT07391033).

29.3.2 Chronic Total Occlusions

Another highly demanding setting where DCB might struggle to demonstrate acceptable results is chronic total occlusion (CTO). Those lesions are usually highly calcific, long, and associated with diffuse coronaries atherosclerosis. In this setting, DES is the most desirable technology applicable due to the acute need for reliable scaffolding and the high rate of acute recoil following lesion preparation. Despite these considerations, DES has some limitations. As per the highly calcified lesions, even in the CTO context, DES underexpansion might be a limitation to achieving an optimal result. Moreover, due to the prolonged occlusion of the vessel, following lesion preparation, it is often tricky to precisely identify the real reference vessel diameter, leading to subsequent potential DES malapposition and implantation of stents that are smaller than the real native vessel diameter. In fact, the use of BMS/DES in CTO lesions has been linked to a higher rate of cardiac events as compared to non-CTO lesions [19]. Although the efficacy of DCB in such lesions has not been extensively investigated, it may be considered as a reasonable option if the stent is not expected to be adequately expanded [20]. Furthermore, patients with CTO often have a relevant burden of comorbidities that place them at high bleeding risk [21–24].

Therefore, the use of DCB might shorten the implanted metal, reducing complications associated with the stent itself, such as in-stent restenosis/thrombosis and long-term antiplatelet therapy. A German multicenter study was the first to show the applicability of DCB in the treatment of CTO, highlighting a high rate of recanalization and a low rate of restenosis [25]. Encouraging results also emerged from a Korean study, which highlighted how the LLL in the DCB group was lower than in the DES group [26]. Since CTO patients often have multiple lesions and previous studies have demonstrated that the number/length of stents is associated with adverse events, some studies have tested hybrid strategies to potentially reduce the stent burden. PEPCAD-CTO compared DES and DCB combined with BMS for treating CTO: although the study found no significant difference in clinical endpoints, the group treated with DCB combined with BMS required a shorter dual antiplatelet regimen and did not experience late in-stent thrombosis [27]. A recent prospective, observational, multicenter study compared the outcomes of "less DES strategy" (DCB alone or combined with DES) and "DES-only strategy" in treating de novo coronary CTO: in the DCB group, the average stent length per lesion and LLL were significantly lower compared with the DES-only group. There were no significant differences in restenosis occurrence between the two groups [28]. A retrospective study also tested a DCB-only strategy and a hybrid strategy (DCB in combination with DES), showing that the recanalization results and long-term outcomes are comparable between the two groups [29]. Although clinical data are limited, the initial evidence points towards a synergistic hybrid treatment strategy based on the combination of DCB plus DES, reducing the total stent length and maintaining the scaffolding properties of stents where it is mandatory. Additionally, DCB allows natural enlargement of the open vessel after PCI, which is the major limitation of stenting in CTO lesions [16]. The European Registry of Chronic Total Occlusion (ERCTO) involving 40,449 cases noted increased use of DCB (from 3.4% in 2016 to 15% in 2023), with favorable outcomes including lower total stent length, reduced contrast usage, and decreased incidence of pericardial tamponade [30].

29.3.2.1 Future Directions for CTO

The final results of the multicenter, international PICCOLETO X study, the largest study on DCB in CTO, have been presented in 2006 [31] PICCOLETO X was a multicenter, ambispective, all-comer international registry including consecutive CTO patients treated with DCB with/out stents. In the 938 patients enrolled the primary endpoint, target vessel failure (TVF) at 12 months, occurred in 9.5% of the patient population, with no differences between DCB-only and blended strategies after PSM (6.2% vs. 8.8%, p=0.367), showing the safety and efficacy of this approach in a selected population with CTO.

29.4 Pipeline of Future Studies on DCB Technology

The introduction of DCB technology in the United States has further increased the need for high-quality clinical evidence, leading to an increase in clinical trials focusing on various lesion types other than ISR, like de-novo, bifurcation lesions, and high bleeding risk (HBR). An overview of the *ongoing and planned clinical trials* evaluating DCB in de novo, ISR, and HBR coronary artery disease (CAD) is provided in Table 29.1.

Bifurcation lesions represent an emerging field for DCB application. Trials such as Hybrid-DEB, HYBRID MAIN, AGENT DCB STANCE, PICCOLETO V, and the EBC DCB trial are assessing DCB-based strategies compared with drug-eluting stent approaches, whereas PROMISE-BIF and Sirolimus DEB in bifurcation (NCT04896177) are comparing the SCB versus PCB (Table 29.2).

The findings of these ongoing studies are expected to contribute to future recommendations and may influence clinical practice in interventional cardiology.

Table 29.1 Clinical trials still evaluating DCB in De novo, ISR, and HBR CAD, by early 2026

Trial name/NCT	Countries	Study Design	Comparison	Condition	Primary Endpoint
CAGE-FREE III trial NCT05209412	China	RCT multicenter, open-label, non-inferiority	PCB versus DES	De novo CAD (large vessels)	FFR at 1 year
DES vs DCB in calcified de novo lesions NCT05750771	China	RCT single-center, open-label, non-inferiority	PCB versus DES	De novo calcified lesions (elderly)	LLL at 1 year
REVERSE trial NCT05846893	Korea; Taiwan; Malaysia; Singapore	RCT multicenter, open-label, non-inferiority	PCB versus DES	De novo CAD (large vessels)	NACE at 1 year
DEBORA study NCT06448637	Spain	RCT multicenter, open-label	DCB versus DES	De novo CAD (large vessels)	Positive vasomotor response at 8 months
MAGICAL SV (MagicTouch™ SCB in small vessels) NCT06271590	North America, Europe, South America	RCT multicenter, single-blind, non-inferiority	SCB versus DES	De novo small vessels (≤2.75 mm RVD)	TLF at 1 year
TRANSFORM II NCT04893291 [32]	Italy, Poland, Bangladesh, Netherlands, France, Spain, Brasil, Thailand, Brunei, Malaysia	RCT multicenter, open-label, non-inferiority	SCB everolimus DES	de novo with RVD 2–3.5, LL <51 mm	TLF at 1 year, and through 5 years
Prevail Global NCT06535854	Global	RCT multicenter, single blind for ISR, open-label for de novo SVD	DCB versus DES for ISR, single arm for SVD	ISR and de novo small vessel disease (SVD)	TLF at 1 year
ISAR-DESIRE 5 NCT05544864	Germany, Spain	RCT multicenter, open-label	DCB versus DES	ISR	MACE at 2 years
MAGICAL ISR NCT05908331	USA	RCT multicenter, single-blind	SCB versus POBA	ISR	TLF at 1 year
Co-CTO NCT04881812	Netherlands	RCT, single-center, single-blind, non-inferiority	DCB versus DES	CTO	%DS at 1 year
DEBATE NCT04814212	Finland, Germany, United Kingdom	RCT multicenter, double-blind, non-inferiority	PCB versus DES	HBR	MACE and BARC 2–5 at 1 year
DCB-HBR NCT05221931	Republic of Korea	RCT multicenter, open-label, non-inferiority	PCB versus DES	HBR	TVF at 2 years
STANCE NCT06959524	USA	RCT multicenter, open-label, de novo (long lesions, bifurcations, SVD)	PCB versus standard of care (DES and/or POBA)	1616 enrolling	TLF at 12 months
PICCOLETO III	USA, Europe	RCT multicenter, open-label, non-inferiority	DCB versus DES	CTO	TLF 1 year
PICCOLETO IV/ EPIC 38 [31]	Spain, Italy, Belgium, Luxemburg	RCT multicenter, open-label, superiority	PCB SAPT versus PCB DAPT	HBR or elderly	MACE 1 year

(continued)

Table 29.1 (continued)

Trial name/NCT	Countries	Study Design	Comparison	Condition	Primary Endpoint
PICCOLETO VII	Italy, Singapore, Spain, United Kingdom, Poland	RCT multicenter, open-label, non-inferiority (core lab)	PCB versus SCB versus DES	SVD	Radial wall strain 6–9 months
PICCOLETO IX/ PHENO NCT07390994	Italy, Spain, United Kingdom, France Poland	Cohort (phenotyping by OCT and correlation with clinical outcome)	DCB	de novo	TLF 1 year
PICCOLETO XI NCT07391033	Italy, Singapore, Spain, United Kingdom, France Poland	Multicenter, open-label, comparison of cutting vs scoring balloons	DCB	ISR (Cohort A); de novo (Cohort B)	TLF 1 year

DCB drug-coated balloon, *DES* drug-eluting stent, *PCB* paclitaxel-coated balloon, *SCB* sirolimus-coated balloon, *CAD* coronary artery disease, *SVD* small vessel disease, *CTO* chronic total occlusion, *ISR* in-stent restenosis, *POBA* plain old balloon angioplasty, *FFR* fractional flow reserve, *LLL* late lumen loss, *DS* diameter stenosis, *RVD* reference vessel diameter, *TLF* target lesion failure, *TLR* target lesion revascularization, *TVF* target vessel failure, *TV-MI* target vessel myocardial infarction, *MACE* major adverse cardiovascular events, *NACE* net adverse clinical events, *HBR* high bleeding risk, *BARC* Bleeding Academic Research Consortium, *IDE* investigational device exemption, *ZES* zotarolimus-eluting stent, *EES* everolimus-eluting stent

Table 29.2 Clinical trials evaluating DCB in bifurcation lesions

Trial name/NCT	Countries	Study Design	Comparison	Population status	Primary Endpoint
Sirolimus DEB in bifurcation lesions NCT04896177	China	Multicenter, open-label, non-inferiority Non-LM bifurcations	SCB versus PCB	280 enrolling	%DS of target lesion branch at 9 months
PROMISE-BIF NCT04918615	China	Multicenter, open-label, non-inferiority Non-LM bifurcations	SCB versus PCB	236 unknown	%DS of side branch at 9 months
Hybrid-DEB NCT05731687	Netherlands	Multicenter, single-blind, non-inferiority Non-LM bifurcations	SCB versus DES	500 unknown	MACE at 2 years
HYBRID MAIN NCT07159737	Malaysia	RCT multicenter Unprotected LM	Hybrid strategy (DES + DCB approach) versus 2-stent	800 unknown	TLF at 2 years
EBC DCB (European Bifurcation Club) NCT06822322	Europe	RCT multicenter, non-inferiority Non-LM bifurcations	DCB strategy versus Stepwise provisional DES strategy	750 enrolling	BOCE at 1 year
PICCOLETO V NCT07391033	Poland, Romania, France, Bahrain, Singapore	RCT multicenter, non-inferiority Non-LM bifurcations	PCB vs SCB vs provisional stenting	321 recruiting	Angio-physiological and CT scan endpoint at 9 months

DCB drug-coated balloon, *DEB* drug-eluting balloon, *SCB* sirolimus-coated balloon, *PCB* paclitaxel-coated balloon, *DES* drug-eluting stent, *POBA* plain old balloon angioplasty, *CAD* coronary artery disease, *MACE* major adverse cardiovascular events, *TLF* target lesion failure, *DS* diameter stenosis, *BOCE* bifurcation-oriented composite endpoint, *MV* main vessel, *SB* side branch

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