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Comprehensive Review

Coronary Drug-Coated Balloons for De Novo and In-Stent Restenosis Indications

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ABSTRACT

Drug-coated balloons are approved outside the United States, not only for the treatment of peripheral arteries but also for coronary arteries. This review describes the technological basics, the scenarios of clinical application, and the current available data from clinical trials for the different coronary indications.

Introduction to drug-coated balloon technology

In the late 1990s, several research groups were working on local drug delivery for vascular treatment.[1–3] By then, it was not yet clear that stents would become the preferred platform. The research group in Tübingen, Germany, very extensively conducted experimental studies on the local administration of paclitaxel in a liquid solution, preferably by porous or double balloon as a delivery tool.[1,2] They were able to show that a relatively short-term exposure of the vessel wall to paclitaxel leads to an inhibition of neointimal formation after experimental vascular treatment. Later, in a clinical trial, this approach resulted to be an effective treatment for in-stent restenosis (ISR).[4]

Creel et al[3] demonstrated that paclitaxel has specific binding to hydrophobic sites within the arterial tissue. They demonstrated that serum proteins increase paclitaxel levels in solution but hinder distribution through tissues.[5] Later, Ulrich Speck and Bruno Scheller pursued a different approach based on x-ray contrast agents as carriers for antiproliferative drugs. They found that injection of a contrast agent-taxane formulation, into the coronary arteries after experimental stent implantation resulted in a dose-dependent reduction of neointimal formation.[6,7] It was also shown that the contrast agent substantially improved the transfer of paclitaxel into the vessel wall.[8] However, the disadvantage of this approach was that it was difficult to predict the dose delivered to a specific vascular territory. This may explain the inferior clinical effectiveness of an iopromide-taxane formulation when compared with that of the device-based approach.[9]

The basic concept of drug-coated balloons (DCB) was born in 2000. Experience with the contrast media-taxane formulation had shown that it is possible to achieve a long-lasting biological effect despite a short contact time.[1] However, a lesion-specific approach would be required and a balloon angioplasty catheter could permit the delivery of an antiproliferative drug without implantation of a permanent device. It was also clear to Speck and Scheller that one or more excipients in addition to the active substance are necessary.[10] In an initial animal study, balloon coating with only paclitaxel and a solvent had no effect in the porcine coronary stent model.[11] By contrast, coating with paclitaxel and the x-ray contrast agent iopromide as excipient showed a pronounced, dose-dependent reduction of neointimal formation even after 4 weeks.[11]

The selection of an appropriate excipient resulted to be crucial for the clinical effectiveness of DCB technology. The coating procedure had to address several relevant factors that could influence an efficient delivery of the antiproliferative medication, such as homogeneity of the coating, crystalline versus amorphous state, drug loss in blood, transfer efficiency on contact with the vessel wall, and particle loss.[12] For these reasons, a variety of additional experimental studies focusing on optimal balloon inflation time,[13] long-term safety,[14] drug persistence in tissue,[15] optimal dose,[16] and alternative coating formulations was conducted.[12,16–19] Different coating variants and dosages resulted in changes in both acute drug transfer and persistence of the drug in the tissue, with implications for a longer-term antirestenotic efficacy.[12,20,21]

The high lipophilicity and favorable binding properties of paclitaxel made it the only drug used in DCBs for a long-time. However, the

Abbreviations: ISR, in-stent restenosis; DES, drug-eluting stent; DCB, drug-coated balloon; BMS, bare metal stent; SVD, small vessel disease; TLR, target lesion revascularization.

Keywords: drug-coated balloon; lesion preparation; paclitaxel; sirolimus.

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effectiveness and safety of sirolimus and its analogs on drug-eluting stents (DES) promoted the development of novel technologies.[12,20,21] Some sirolimus-coated balloons are currently approved for clinical use in certain countries, and early small trials showed noninferior outcomes compared with those of paclitaxel-coated balloons.[22,23] Preclinical studies with zotarolimus-coated balloons showed promising findings and, more recently, a biolimus-coated balloon was approved for clinical use.[24–26]

This review aimed to present the main procedural aspects and clinical indications of DCB angioplasty, comprehensively summarize highest quality evidence accrued and recent promising data, and critically analyze residual areas of uncertainty.

DCB angioplasty

The rationale for angioplasty with DCB relies on the potential advantage of delivering an antiproliferative medication without implantation of a permanent metallic device.[1,2,11,27] The antiproliferative effects of the drug delivered on the endothelial tissue reduces exaggerated neointimal hyperplasia after coronary artery disease treatment–related vessel wall injury and the absence of permanent metallic implants offers several potential advantages over the midterm and long-term, including a mitigation of stent-related mechanisms leading to restenosis, thrombosis, and accelerated neoatherosclerosis.[1,2,11,27–31] In this regard, some specific settings are associated with higher rates of restenosis and thrombosis after stenting than those with more common and less complex patterns of coronary artery disease. ISR, small-vessel disease, and bifurcation disease involving the side branch ostium are typical settings where the implantation of stents may not lead to sustained successful revascularization at a midterm or long-term follow-up.[32–34]

DCBs are generally rapid-exchange semicompliant balloon catheters with the surface coated with a formulation such as an antiproliferative drug—mainly paclitaxel and more recently sirolimus—combined with an excipient or carrier that regulates and facilitates the delivery.[11,27] The primary mechanism of the antirestenotic effect of paclitaxel and sirolimus is inhibition of cell division, ultimately leading to decreased neointima formation.[35] Paclitaxel acts through a blockade of cell-cycle progression during mitosis by irreversible binding to and stabilizing microtubules.[36] By contrast, the immunosuppressive and cell proliferation inhibitory effect of sirolimus (rapamycin) results from its formation of a complex with an intracellular cytosolic protein (FKBP12) that binds to a 282-kDa serine/threonine protein kinase, reversibly inhibiting this protein, called mTOR (mammalian target of rapamycin).[37] Preclinical studies have demonstrated that DCB technology allows an effective local intracellular drug transfer in only 30 to 60 seconds of contact between the inflated balloon catheter and the vessel surface.[27,38,39] The short time of contact between device and vessel wall has proven to be sufficient to transfer an appropriate amount of drug inside the endothelial cells and available coatings preserve medication on DCB before delivery.[11,39,40]

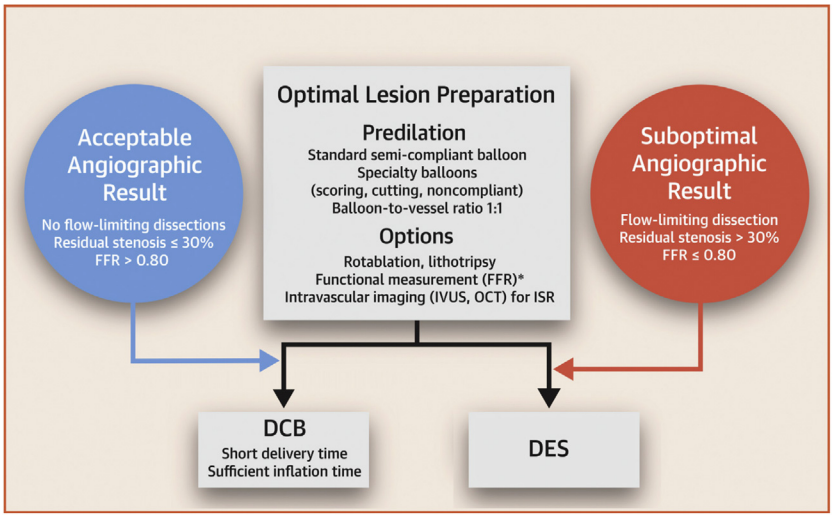
Coating constituents significantly differ across devices with consequent changes in appearance from transparent to opaque and dusty white as the covering varies from resinous to multilayered and crystalline, respectively.[27,41] Clinically proven carriers are iopromide, a low-osmolality contrast medium, and urea, an endogenous metabolite.[6,27,41,42] Devices developed later used other spacers, such as shellac, butyryl-tri-hexyl citrate, acetyl-tri-butyl citrate, resveratrol, and polyethylene glycol.[27,39,41] Difference in coating constituents across DCBs provide partial explanation for the absence of a class effect for either paclitaxel-coated or sirolimus-coated balloon.[21,43–45]

De novo coronary artery disease

DCBs have been tested across different clinical and anatomic settings of de novo coronary artery disease with mixed results and different strength of evidence.[46] Over the past decade, the indication of DCB angioplasty for small-vessel disease has become more robust owing to a growing number of clinical studies. By contrast, treatment with DCBs in other settings, such as bifurcation disease and acute coronary syndrome culprit lesions, is supported by fewer studies, and further analysis is warranted to confirm some promising findings. In general, the treatment of de novo lesions following the concept of DCB-alone strategy accepts an inferior angiographic acute gain compared with that of stenting (Central Illustration), with a subsequent compensation of this advantage at follow-up primarily by reduced late lumen loss and, sometimes, positive remodeling.[30,47–50]

Small vessel

The treatment of small coronary artery segments is associated with higher rates of periprocedural and long-term major adverse cardiovascular events irrespective of the interventional strategy used.[51,52]



Central Illustration.
DCB-only treatment algorithm according to the international DCB consensus group.[91] DCB, drug-coated balloon; DES, drug-eluting stent; FFR, fractional flow reserve; ISR, in-stent restenosis; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Early investigations showed that bare-metal stent (BMS) implantation in vessel segments with a smaller diameter significantly increased rates of ISR at the angiographic follow-up.[51,52] Despite DES introduction has reduced the incidence of target lesion revascularization (TLR) in small vessels, this anatomic subset continues to be associated with technical issues and worse outcomes.[33,53,54]

Against this background, DCB angioplasty for small-vessel disease is an attractive treatment option that may reduce both restenosis and target lesion thrombosis by avoiding the implantation of a permanent metallic layer. Several clinical studies on DCBs were conducted with the objective to address these hypotheses (Table 1), and the definitions used to identify small vessels generally included coronary segments with reference diameter ≤2.75, <2.80, or ≤3.00 mm, depending on the study.[55–60]

Early findings from the prospective, single-arm PEPCAD (Paclitaxel-Eluting PTCA-Balloon Catheter to Treat Small Vessel Coronary Artery Disease) study suggested that angioplasty with DCB for de novo small-vessel disease was associated with a favorable safety and efficacy at 12 months.[60] In this study, patients who did not require bailout stenting with BMS showed at 12 months an incidence of cardiac death, target vessel myocardial infarction, or TLR of 6.1%.[60] Of note, these favorable results remained unchanged at 36 months because no additional target lesion–related events occurred after 12 months.[61]

Later, the PICCOLETO (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) trial comparing an early iteration of a paclitaxel-coated balloon with a traditional paclitaxel-eluting stent showed contrasting conclusions.[56] In this trial, treatment with DCB was associated with a significant increase in percentage diameter stenosis at the angiographic follow-up.[56] These unfavorable results led to an anticipated termination of the trial.[56]

Against this uncertain background, the pivotal BELLO (Balloon Elution and Late Loss Optimization) trial, including 182 patients with small-vessel disease randomly assigned to DCB angioplasty or paclitaxel-eluting stent implantation, showed that at the 6-month angiographic follow-up, DCB resulted to be not only noninferior but also superior to DES in the primary end point of late lumen loss (0.08 ± 0.38 mm vs 0.29 ± 0.44 mm; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .001$).[58] However, the trial was designed to prove only noninferiority and rates of bailout BMS implantation were as high as 20%.[58] In-segment binary restenosis (10.0% vs 14.6%; $P = .35$) and TLR (4.4% vs 7.6%; $P = .37$) were not significantly different between the groups, but the trial had an insufficient statistical power to test these secondary end points.[58] Of note, at 12 months no safety concerns related to DCB technology were observed, and the subsequent 24-month analysis showed that the cumulative incidence of all-cause death, myocardial infarction, or target vessel revascularization was significantly lower in the DCB group (14.4% vs 30.4%; $P = .015$).[62] At 24 months, the rates of TLR (6.8% vs 12.1; $P = .23$) and target vessel revascularization (10.2% vs 17.6%; $P = .16$) continued to be not significantly different between the groups. At 36 months, the Kaplan-Meier method showed a statistically significant difference in major adverse cardiac event (MACE) between the groups (DCB 14.4% vs PES 30.4%; $P = .015$).[62] In the same period, a small randomized clinical trial comparing 135 patients with small-vessel disease assigned to DCB angioplasty or plain balloon angioplasty in a 2:1 ratio was performed.[31] Although no significant difference between the treatments was observed for the primary end point of cardiac death, target vessel myocardial infarction, or TLR, at the 6-month angiographic follow-up, DCB angioplasty was associated with a lower late lumen loss than plain balloon angioplasty (0.01 ± 0.31 vs 0.32 ± 0.34 mm; $P < .01$).[31] There was also a numerical trend toward a reduced incidence of TLR with DCB (3.4% vs 10.3%; $P = .20$), but the difference was not statistically significant owing to the limited statistical power.[31]

More recently, in the BASKET-SMALL 2 (Basel Kosten Effektivitäts Trial-DCBs versus Drug-eluting Stents in Small Vessel Interventions 2) trial, 758 patients were randomly assigned to DCB angioplasty or DES after adequate lesion preparation resulting in a residual stenosis of ≤30%, a thrombolysis in myocardial infarction 3 flow grade, and National Heart, Lung, and Blood Institute dissection grade of ≤B.[57] Fourteen percentage of patients with de novo stenosis were not amenable to randomization owing to suboptimal angiographic results after predilation.[57] The trial was powered to assess the noninferiority of DCB regarding a composite end point of MACEs such as cardiac death, nonfatal myocardial infarction, or target vessel revascularization at 12 months in the per-protocol cohort.[57] Approximately 25% of patients received paclitaxel-eluting stents, and the remaining a second-generation everolimus-eluting stent.[57] At 12 months, DCB angioplasty was noninferior to DES implantation in the per-protocol cohort ($P_{\text{noninferioty}} = .022$).[57] The results of the intention-to-treat analysis were consistent ($P_{\text{noninferioty}} = .037$; 7.5% vs 7.3%; HR, 0.97; 95% CI, 0.58-1.64).[57] The incidence of the individual end points of cardiac death (3.1% vs 1.3%; HR, 2.33; 95% CI, 0.82-6.61), nonfatal myocardial infarction (1.6% vs 3.5%; HR, 0.46; 95% CI, 0.17-1.20), and target vessel revascularization (3.4% vs 4.5%; HR, 0.75; 95% CI, 0.36-1.55) did not significantly differ between DCB angioplasty and DES implantation.[57] Three-year follow-up results remarkably showed that both DCB and DES were associated with an incidence of cardiac death, nonfatal myocardial infarction, and target vessel revascularization of 15% (HR, 0.99; 95% CI, 0.68-1.45) (Figure 1).[63] The individual end points of cardiac death (5% vs 4%; HR, 1.29; 95% CI, 0.63-2.66), nonfatal myocardial infarction (6% vs 6%, HR, 0.82; 95% CI, 0.45-1.51), and target vessel revascularization (9% vs 9%; HR, 0.95; 95% CI, 0.58-1.56) were not significantly different between the groups.[63] The results were consistent in subgroup analyses of diabetes mellitus,[64] acute coronary syndrome,[65] renal failure,[66] and high bleeding risk (HBR) with a concomitant trend toward lower bleeding risk[67] and significantly fewer vascular occlusions after DCB.[68] However, because of additional interventions with DES at other lesions in larger vessels, the theoretical benefits of DCB are not simple to demonstrate in combined clinical end points.[69]

The RESTORE SVD (RESTORE Small Vessel Disease) trial, including 230 patients presenting with de novo disease of small vessels randomized to paclitaxel-coated balloons or second-generation zotarolimus-eluting stents, showed at the 9-month angiographic follow-up that DCB angioplasty was noninferior to DES implantation regarding the primary end point of in-segment percentage diameter stenosis (29.6% ± 2.0% vs 24.1% ± 2.0%, $P_{\text{noninferiority}} < .001$).[59] Results were unchanged at per-lesion and as-treated analyses.[59] However, the DCB group exhibited a smaller in-segment minimum lumen diameter (1.40 ± 0.42 mm vs 1.71 ± 0.39 mm; $P < .001$) and similar late lumen loss (0.25 ± 0.42 mm vs 0.27 ± 0.36 mm; $P = .73$) than the DES group.[59] At 12 and 24 months, there were no differences between DCB and DES in cardiac death, target vessel myocardial infarction, or TLR (4.4% vs 2.6%; $P = .73$ and 5.2% vs 3.7%; $P = .75$, respectively) and in each individual component of the composite end point.[59,70]

Data from large-scale registries comparing DCBs with second-generation DES for the treatment of de novo small-vessel disease have shown contrasting results. Several small registries have shown that DCB angioplasty for small-vessel disease is associated with safety and efficacy similar to DES implantation.[71,72] By contrast, in a report from the SCAAR (Swedish Coronary and Angioplasty Registry) including 14,778 consecutive patients presenting with de novo coronary artery disease of small vessels who received treatment with paclitaxel-based DCBs (2503 devices) or second-generation DES (33,038 devices) for the treatment of de novo coronary artery.[73] A device-level propensity score weighted analysis showed that at 3 years, clinically significant restenosis occurred more frequently after DCB angioplasty than DES implantation (adjusted HR, 2.03; 95% 1.54-2.67), whereas target lesion thrombosis did not significantly differ between the treatments (adjusted HR, 0.74; 95% 0.41-1.33).[73] A patient-level propensity score weighted analysis showed that at 3 years all-cause death and myocardial infarction were not significantly different between the groups (adjusted HR, 1.18; 95% CI, 0.99-1.40, and adjusted HR, 1.25; 95% CI, 0.96-1.63, respectively).[73]

Table 1. Main randomized clinical trials comparing drug-coated balloon with drug-eluting stent for the treatment of small-vessel disease.

	PICCOLETO		BELLO		BASKET-SMALL 2		RESTORE SVD		PICCOLETO II	
Vessel size	≤2.75		<2.80		2.00-3.00		2.25-2.75		≤2.75	
Sample size	57		182		758		230		232	
DCB	Paclitaxel microcrystals on nanoporous surface		Urea-paclitaxel		Iopromide-paclitaxel		Shellac-paclitaxel		Dextran-paclitaxel	
DES	Paclitaxel-eluting durable-polymer stainless steel (97 μm)		Paclitaxel-eluting durable-polymer stainless steel (97 μm)		Paclitaxel-eluting durable-polymer platinum-chromium (81 μm) and Zotarolimus-eluting durable-polymer cobalt-chromium (91 μm)		Zotarolimus-eluting durable-polymer cobalt-chromium (91 μm)		Everolimus-eluting durable-polymer cobalt-chromium (81 μm)	
Primary end point	In-lesion % diameter stenosis		In-lesion late lumen loss		Cardiac death, nonfatal myocardial infarction, or target vessel revascularization		In-segment % diameter stenosis		In-lesion late lumen loss	
Primary follow-up, mo	6		6		12		9		6	
Angiographic follow-up	Yes		Yes		No		Yes		Yes	
Maximum follow-up, mo	9		36		36		24		12	
Design	Noninferiority		Noninferiority		Noninferiority		Noninferiority		Noninferiority	
Period	August 2007- August 2008		Before July 2012		April 2012- February 2017		August 2016-June 2017		May 2015-May 2018	
Region	Italy		Italy		Switzerland, Germany, and Austria		China		Italy and Spain	
Centers	1		15		14		12		5	
Registration[a]	EudraCT 2009-012268-15		NCT01086579		NCT01574534		NCT02946307		NCT03899818	
	DCB	DES	DCB	DES	DCB	DES	DCB	DES	DCB	DES
Patients/lesions[b]	28/28	29/29	90/81	92/82	382	376	116/100	114/93	118/105	114/104
In-segment % diameter stenosis	43.6 ± 27.4[c]	24.3 ± 25.1[c]	35.0 ± 16.0	33.3 ± 20.0	—	—	29.3 ± 20.2	23.9 ± 15.9	36.6 ± 21	32.2 ± 19
In-segment late lumen loss	NA	NA	0.05 ± 0.37	0.17 ± 0.45	—	—	0.25 ± 0.42	0.27 ± 0.36	0.01 ± 0.25[c]	0.14 ± 0.38[c]
In-segment binary restenosis	9 (32.1)[c]	3 (10.3)[c]	8 (10.0)	12 (14.6)	—	—	11 (11.0)	8 (8.6)	11 (10.5)	10 (9.6)
Target lesion revascularization	9 (32.1)	3 (10.3)	6M: 4 (4.4) 36M: 6 (6.7)	6M: 7 (7.6) 36M: 12 (13.0)	NA	NA	12M: 5 (4.4) 24M: 6 (5.2)	12: 3 (2.6) 36: 3 (2.8)	6 (5.6)	6 (5.6)
Target lesion thrombosis	0	0	6M: 0 36M: 0	6M: 0 36M: 0	12M: 2 (1) 36M: 2 (1)	12M: 4 (1) 36M: 6 (2)	12M: 0 24M: 0	12M: 0 36M: 0	0	2 (1.9)
MACE[d]	10 (35.7)	4 (13.8)	6M: 9 (10.0) 36M: 13 (14.4)[c]	6M: 15 (16.3) 36M: 28 (30.4)[c]	12M: 28 (8) 36M: 53 (15)	12M: 28 (7) 36M: 53 (15)	12M: 11 (9.6) 36M: 14 (12.2)	12M: 11 (9.6) 36M: 14 (12.2)	6 (5.6)	8 (7.5)
Dual antiplatelet therapy	Stable angina: 1 mo (3 mo for bailout stenting) Unstable angina: 12 mo	12 mo	1 mo (3 mo for bailout stenting)	12 mo	Stable angina: 1 mo (3 mon for bailout stenting with BMS and 6 mo for bailout stenting with DES) Acute coronary syndrome: 12 mo	Stable angina: 6 mo Acute coronary syndrome: 12 mo	≥6 mo	≥6 mo	Stable angina: 1 mo Acute coronary syndrome: 12 mo	Stable angina: 6 mo Acute coronary syndrome: 12 mo
Main conclusions	DCB angioplasty showed a lower antirestenotic efficacy than DES implantation		DCB angioplasty was associated with improved angiographic and clinical results compared with DES implantations		DCB angioplasty was associated with similar clinical effectiveness and safety compared with DES implantation		DCB angioplasty was associated with noninferior angiographic effectiveness compared with DES implantation		DCB angioplasty is associated with a lower late lumen loss than DES implantation	

Late lumen loss and percentage diameter stenosis are means and standard deviations. Binary restenosis and clinical outcomes are counts and rates.
MACE, major adverse cardiac events; NA, not available.

[a] Registration in ClinicalTrials.gov except for the PICCOLETO trial that was registered with the European Union Drug Regulating Authorities Clinical Trials Database registry. [b] Patients analyzed at the clinical follow-up/lesions analyzed at the angiographic follow-up. [c] Significant differences. [d] 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, nonfatal 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.

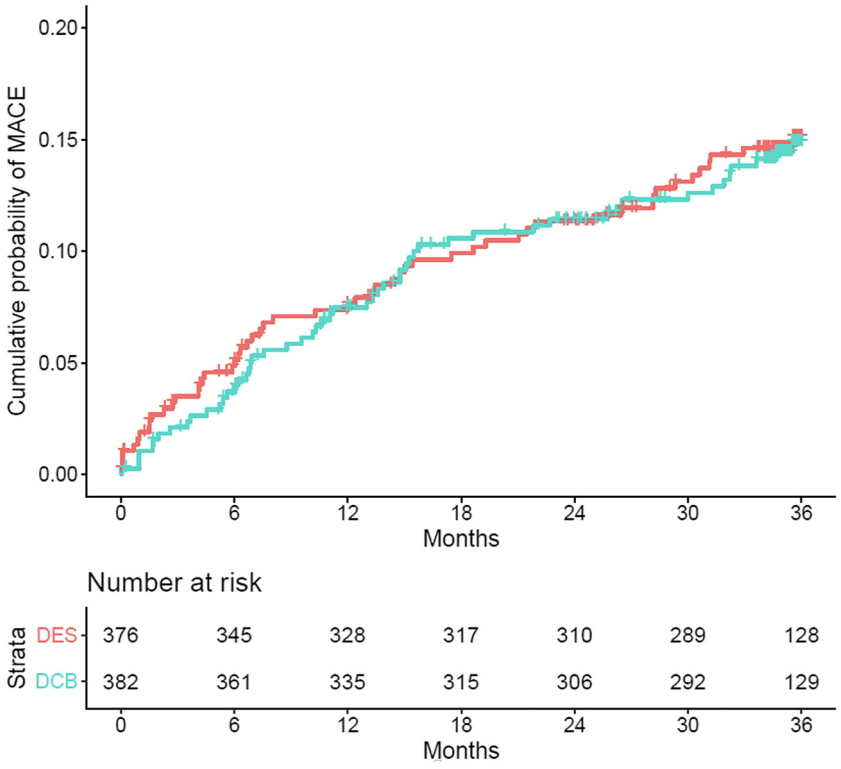


Figure 1.
Kaplan-Meier estimates of the cumulative probabilities of major adverse cardiac events in the 2 study groups during 3 years for the full-analysis set of the BASKET-SMALL 2 trial.[63] DCB, drug-coated balloon; DES, drug-eluting stent; HR, hazard ratio.

Finally, the latest trial on the topic, namely the PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment II) trial, showed that at a median angiographic follow-up of 189 days, a paclitaxel-coated balloon was noninferior and superior to a second-generation everolimus-eluting stent in the primary end point of in-lesion late lumen loss (0.04 ± 0.28 mm vs 0.17 ± 0.39 mm; $P_{noninferiority}$ = .001; $P_{superiority}$ = .03).[55] In-lesion binary restenosis (6.5% vs 6.3%; P = .98) and percentage diameter stenosis (21.6% ± 13% vs 25.1 ± 11%; P = .37) were not significantly different between DCB and DES.[55] Results in-segment were consistent for each end point.[55] At 12 months, the composite end point of cardiac death, myocardial infarction, or TLR (7.5% vs 5.6%; P = .51) and the individual end point of TLR (5.6% vs 5.6%; P = .80%) were not significantly different between DCB and DES.[55]

The interpretation of differences in available evidence on DCBs for small-vessel disease is challenging and likely multifactorial. First, some inconsistent results of studies testing different types of DCB may suggest the absence of a class effect with a higher antirestenotic performance of some devices due to differences in excipients and catheter properties.[56–59,74] Second, the absence of accurate lesion predilation may explain some large differences across trials. In the PICCOLETO trial, only 25% of patients assigned to DCB received predilation, whereas in subsequent investigations, much more attention was given to lesion preparation, and suboptimal results of residual stenosis before DCB application were included among exclusion criteria.[56,57] Finally, some unmeasured clinical and angiographic characteristics of patients may have played a role in producing dissimilar findings across investigations.

Bifurcation

Coronary bifurcation disease is observed in up to 20% of percutaneous coronary interventions.[75] Treatment of bifurcation lesions remains fraught by suboptimal results, particularly at the level of the side branch, which set the main rationale of studies investigating DCB in this setting.

Initial randomized clinical trials explored the combination DCB plus BMS for the treatment of coronary bifurcation lesions with unfavorable results.[76,77] In the DEBIUT (Drug-Eluting Balloon in Bifurcations Trial), 117 patients were 1:1:1 randomly assigned to DCB angioplasty of both branches, followed by BMS implantation in the main vessel, BMS implantation in the main vessel and plain balloon angioplasty of the side branch, or paclitaxel-DES implantation in the main vessel and plain balloon angioplasty of the side branch.[76] Kissing balloon after provisional stenting was recommended regardless of the strategy assigned.[76] At the 6-month angiographic follow-up, the strategy based on DCB failed to show significant differences compared with the BMS-based strategy and resulted to be less effective than the DES-based strategy.[76] In the BABILON (Paclitaxel-Coated Balloon in Bifurcated Lesions) trial, 108 patients were randomized to sequential predilation and DCB angioplasty of both branches, followed by provisional BMS implantation of main branch or sequential predilation of both branches, then by provisional everolimus-eluting stent implantation of the main branch.[77] The DCB plus BMS strategy was associated with a 9-month in-segment late lumen loss (0.31 ± 0.48 mm vs 0.16 ± 0.38 mm; $P_{noninferiority}$ = .001, $P_{superiority}$ = .15) noninferior to the DES-alone strategy.[77] Of note, the side branch late lumen loss was not significantly different between DCB and DES (−0.04 ± 0.76 mm vs −0.03 ± 0.51 mm; P = .983). However, an increased incidence of TLR (13.5% vs 1.8%; P = .027), mainly driven by main branch restenosis, and a numerical excess of major adverse cardiac events (17.3% vs 7.1%; P = .105).[77]

Other studies focused on the potential benefit of DCB angioplasty for the treatment of the side branch after DES implantation in the main branch. In a trial, 64 patients with bifurcation disease involving the side branch and/or the distal component of main branch were randomized after predilation to DCB angioplasty of the side branch or no further

treatment.[78] Postprocedural angiographic results were similar between the groups, but at the 9-month angiographic follow-up, in-lesion late lumen loss (0.13 ± 0.31 mm vs 0.51 ± 0.66 mm; $P = .013$), minimum lumen diameter (1.78 ± 0.37 mm vs 1.39 ± 0.80 mm; $P = .015$), and binary restenosis (5.9% vs 25.7%; $P = .045$) were significantly lower in patients treated with DCB.[78]

In a registry encompassing 127 patients, ~54% of all bifurcations could be treated by DCB-alone strategy with low event rates at 9 months and no thrombosis.[79] Another small observational study, testing a combined strategy for the treatment of bifurcation disease by implantation of a dedicated stent in the main branch and application of a DCB in the side branch, showed a low side branch late lumen loss and TLR a 6-month follow-up.[80]

Despite some interesting preliminary findings, whether strategies for bifurcation lesions using a DCB, alone or in combination with DES, can produce comparable with or superior outcomes than conventional DES-based strategies is unclear, and a higher quality evidence is still required.

Acute coronary syndrome

The rationale for a DCB-based strategy in this setting relies on the possible observation of limited-extent or nonsignificantly obstructive ulcerated lesions, causing an acute coronary syndrome and the frequent selection of stents with an inappropriate size owing to acute-phase dynamic vessel wall changes, mainly vasoconstriction and plaque remodeling. Restoring a normal epicardial blood flow by DCB angioplasty associated with dual antiplatelet therapy with potent $P2Y_{12}$ inhibitor and planning a subsequent angiography, followed by percutaneous coronary intervention with DES, in case of suboptimal results may be an attractive, conservative treatment strategy in some patients. However, the presence of significant thrombus should discourage from using DCBs for the potential risk of abrupt vessel closure due to the absence of thrombotic entrapment by stenting and a possible lower antirestenotic effectiveness of DCBs owing to limitations in drug delivery when thrombus is interposed between device and vessel wall.

The treatment of acute coronary syndrome lesions by DCB was tested in some investigations. The DEB-AMI (Drug-Eluting Balloon in Acute ST-Segment Elevation Myocardial Infarction) 3-arm trial compared BMS implantation, DCB followed by BMS implantation, and DES implantation in 150 patients presenting with ST-segment elevation acute myocardial infarction.[81] In this trial, DCB followed by BMS implantation failed to show angiographic superiority to the BMS-only and DES groups.[81]

More recently, the PEPCAD NSTEMI (Bare Metal or Drug-Eluting Stent Versus Drug Coated Balloon With Provisional Stenting in Non–ST-Elevation Myocardial Infarction) trial showed that a DCB-only strategy in 210 patients presenting with non–ST-segment elevation myocardial infarction was noninferior to BMS or DES implantation regarding the 9-month occurrence of a composite of cardiac death, myocardial reinfarction, or TLR (3.8% vs 6.6%; $P_{\text{noninferiority}} < .003$; $P_{\text{superiority}} = .53$).[82] No safety concerns emerged regarding the individual end points of cardiac death, myocardial reinfarction, and target lesion thrombosis and results of per-protocol analysis were consistent.[82]

Consistent results were observed the REVELATION (Drug-Coated Balloon Versus Drug-Eluting Stent in Acute Myocardial Infarction) trial.[83] In this trial, 120 patients undergoing primary percutaneous coronary interventions for non–ST-segment elevation myocardial infarction were randomly assigned DCB or DES with the objective of assessing the infarct-related lesion by a fractional flow reserve at 9 months.[83] At the follow-up, no significant differences were observed in the fractional flow reserve between DCB and DES (0.92 ± 0.05 vs 0.91 ± 0.06; $P = .27$), although, eventually, a substantial number of patients were not assessable, and the sample size was limited.[83] Angiographic and clinical end points were not significantly different between the treatment groups.[83] At 2 years, a composite of all-cause death, recurrent myocardial infarction, or TLR occurred in 5.4% of patients assigned to DCB and 1.9% of patients in the DES group (HR, 2.86; 95% CI, 0.30-27.53; $P = .34$).[84]

The subgroup analysis of the BASKET-SMALL 2 trial showed no interaction between acute and chronic coronary syndrome and treatment effect of DCB versus DES in patients with small-vessel coronary artery disease.[65]

High bleeding risk

Several DES trials investigated 1 month of DAPT in patients with HBR.[85–87] The DEBUT trial compared DCB treatment for de novo lesions with BMS implantation in a HBR population. At 9 months, target lesion failure occurred in 14% in the BMS group, comparing well with the corresponding event rates for DES in LEADERS FREE,[85] SENIOR,[86] or ONYX ONE.[87] By comparison, the primary end point in the DCB group of DEBUT occurred only in 4% of cases (1 patient) after 1 year,[88] well below the reported event rates in the stent trials.[85–87] The benefit of DCB therapy was maintained up to 3 years, mainly driven by cardiac mortality and myocardial infarction.

Other settings

Available evidence on a DCB-only strategy for the treatment of de novo disease in large coronary arteries and other settings does not provide concerns related the efficacy and safety.[88–90] However, randomized data on large vessels and high-quality information on other specific clinical and anatomic subsets of de novo coronary artery disease are still lacking.

Late lumen enlargement and vasomotion

Balloon angioplasty alone can rarely achieve a stent-like result. Usually, a residual stenosis remains, which should not exceed 30% after lesion preparation.[91] Subsequently, late lumen enlargement described for paclitaxel-coated ballons[29,92] allows for angiographic results comparable with those of DES after a few months.[93] An increase in the total vessel cross-sectional area has been described as the most important mechanism for lumen improvement.[29,47] In addition, recent data show that there may be a reduction of atherosclerotic plaque area in a portion of patients.[94]

In addition to lumen gain over time, clinical data on vasomotion indicated a possible incremental biological advantage of DCB angioplasty.[95,96] A recent trial showed that endothelial function in treated coronary vessels was better preserved by DCB than that by new-generation DES.[95] Another study concluded that vasomotion after DCB treatment was similar to angiographically normal segments, although this result might have depended on a reasonable extent of residual coronary artery disease.[96]

In-stent restenosis

ISR is traditionally defined as a reduction in the luminal diameter of ≥50% within a previously stented segment or the 5-mm segments proximal and distal to the stent (stent edges).[97] Despite substantial medical and technological advances, approximately 5%-10% of contemporary percutaneous coronary interventions are performed for ISR, and at the long-term follow-up, ISR continues to be primary cause of percutaneous coronary intervention failure.[98,99] Several randomized clinical trials (Table 2), observational studies, and meta-analyses have highlighted the favorable performance of DCBs in patients presenting with ISR.[27,100–104]

Table 2. Main randomized clinical trials comparing DCB with DES for the treatment of in-stent restenosis.

	PEPCAD II		ISAR-DESIRE 3[a]		PEPCAD China ISR		RIBS V		SEDUCE	
ISR type	BMS		DES		DES		BMS		BMS	
Sample size	131		268[a]		215[b]		189		50	
DCB	Iopromide-paclitaxel		Iopromide-paclitaxel		Iopromide-paclitaxel		Iopromide-paclitaxel		Iopromide-paclitaxel	
DES	Paclitaxel-eluting durable-polymer stainless steel (97 μm)		Paclitaxel-eluting durable-polymer stainless steel (97 μm)		Paclitaxel-eluting durable-polymer stainless steel (97 μm)		Everolimus-eluting durable-polymer cobalt-chromium (81 μm)		Everolimus-eluting durable-polymer cobalt-chromium (81 μm)	
Primary end point	In-segment late lumen loss		In-segment % diameter stenosis		In-segment late lumen loss		In-segment minimum lumen diameter		% Uncovered struts[c]	
Primary follow-up, mo	6		6-8		9		6-9		9	
Angiographic follow-up	Yes		Yes		Yes		Yes		Yes	
Maximum follow-up, mo	36		36		24		36		12	
Design	Nonequality		Noninferiority		Noninferiority		Nonequality		Nonequality	
Period	January 2006-Dec 2006		August 2009-October 2011		Mar 2011-April 2012		January 2010- January 2012		June 2009-October 2011	
Region	Germany		Germany		China		Spain		Belgium	
Centers	10		4		17		25		2	
Registration[d]	NCT00393315		NCT00987324		NCT01622075		NCT01239953		NCT01065532	
	DCB	DES	DCB[a]	DES[a]	DCB	DES	DCB	DES	DCB	DES
Patients/lesions[b]	66/57	65/59	137/147	131/142	109/93	106/82	95/84	94/86	25/22	25/22
In-segment % diameter stenosis	29.4 ± 17.5	34.2 ± 24.3	38.0 ± 21.5	37.4 ± 21.8	29.0 ± 21.3	30.8 ± 25.3	24 ± 20[e]	13 ± 17[e]	31.8 ± 14.9	26.6 ± 14.6
In-segment late lumen loss	0.17 ± 0.42[e]	0.38 ± 0.61[e]	0.37 ± 0.59	0.34 ± 0.61	0.46 ± 0.51	0.55 ± 0.61	0.14 ± 0.5	0.04 ± 0.5	0.16 ± 0.49	0.08 ± 0.40
In-segment binary restenosis	4 (7.0)[e]	12 (20.3)[e]	39 (26.5)	34 (23.9)	18 (18.6)	20 (23.8)	8 (9.5)	4 (4.7)	2 (9.1)	1 (4.6)
Target lesion revascularization	12M: 4 (6.3) 36M: 4 (6.3)	12M: 10 (15.4) 36M: 10 (15.4)	12M: 30 (22.1) 36M: 44 (33.3)	12M: 17 (13.5) 36M: 29 (24.2)	12M: 17 (15.6) 36M: 17 (15.9)	12M: 13 (12.3) 36M: 14 (13.7)	12M: 6 (6) 36M: 8 (8)[e]	12M: 2 (2) 36M: 2 (2)[e]	1 (4.2)	2 (8.0)
Target lesion thrombosis	12M: 0 36M: 0	12M: 0 36M: 0	12M: 1 (0.7) 36M: 1 (0.8)	12M: 1 (0.8) 36M: 2 (1.6)	12M: 1 (0.9) 36M: 1 (0.9)	12M: 1 (0.9) 36M: 3 (2.9)	12M: 1 (1) 36M: 1 (1)	12M: 0 36M: 0	0	1 (4.0)
MACE[f]	12M: 6 (9.1) 36M: 23 (34.8)	12M: 14 (21.5) 36M: 27 (41.5)	12M: 32 (23.5) 36M: 51 (38.0)	12M: 25 (19.3) 36M: 48 (37.7)	12M: 26 (23.9) 36M: 27 (25.2)	12M: 25 (23.6) 36M: 31 (30.4)	12M: 11 (12) 36M: 15 (16)	12M: 6 (6) 36M: 10 (11)	NA	NA
Dual antiplatelet therapy, mo	6	12	≥6	≥6	≥6	≥6	3	12	NA	NA
Main conclusion	DCB angioplasty reduced late lumen loss and binary restenosis compared with DES implantation		DCB was associated with noninferior effectiveness compared with DES implantation. At a long-term follow-up, DCB was associated with a trend toward an increased incidence of target lesion revascularization and a reduced mortality compared with DES		DCB angioplasty was associated with noninferior angiographic effectiveness compared with DES implantation. At a long-term follow-up, DCB was associated with a lower mortality than DES		DES was associated with superior angiographic effectiveness and superior long-term incidence of target lesion revascularization compared with DCB		DCB was associated with a lower percentage of uncovered struts at optical coherence tomography follow-up than DES implantation. However, in-stent percentage diameter stenosis at angiographic follow-up was higher after DCB angioplasty than that after DES implantation	

	RIBS IV	TIS	DARE	RESTORE	BIOLUX-RCT
ISR type	DES	BMS	BMS: 120 (45.8) DES: 142 (54.2)	DES	BMS: 86 (35.7) DES: 155 (64.3)
Sample size	309	136	278	172	229
DCB	Iopromide-paclitaxel (3 μg/mm^2)	Iopromide-paclitaxel (3 μg/mm^2)	Iopromide-paclitaxel (3 μg/mm^2)	Iopromide-paclitaxel (3 μg/mm^2)	Butyryl-tri-hexyl citrate-paclitaxel (3 μg/mm^2)
DES	Everolimus-eluting durable-polymer cobalt-chromium (81 μm)	Everolimus-eluting durable-polymer cobalt-chromium (81 μm)	Everolimus-eluting durable-polymer cobalt-chromium (81 μm)	Everolimus-eluting durable-polymer cobalt-chromium (81 μm)	Sirolimus-eluting bioresorbable-polymer cobalt-chromium (60-80 μm)
Primary end point	In-segment late lumen loss	In-segment late lumen loss	In-segment minimum lumen diameter	In-segment late lumen loss	In-segment late lumen loss
Primary follow-up, mo	6-9	12	6	9	6
Angiographic follow-up	Yes	Yes	Yes	Yes	Yes

(*continued on next page*)

Table 2 (*continued*)

	RIBS IV		TIS		DARE		RESTORE		BIOLUX-RCT	
Maximum follow-up, mo	36		36		12		12		18	
Design	Nonequality		Noninferiority		Noninferiority		Nonequality		Noninferiority	
Period	January 2010-August 2013		January 2012- August 2014		May 2010-June 2015		April 2013- October 2016		August 2012- January 2015	
Region	Spain		Czech Republic		the Netherlands		South Korea		Germany and Latvia	
Centers	23		1		8		10		14	
Registration[d]	NCT01239940		NCT01735825		NTR2189		NCT01967199		NCT01651390	
	DCB	DES	DCB	DES	DCB	DES	DCB	DES	DCB	DES
Patients/lesions[b]	154/139	155/133	68/74	68/74	137/105	141/115	86/38	86/36	157/128	72/59
In-segment % diameter stenosis	30 ± 22[e]	23 ± 22[e]	26.2 ± 18.0	30.9 ± 24.6	36.1 ± 15.5	33.8 ± 18.6	34 ± 21[e]	26 ± 15[e]	31.6 ± 12.8	32.0 ± 23.8
In-segment late lumen loss	0.30 ± 0.6[e]	0.18 ± 0.6[e]	0.09 ± 0.44	0.44 ± 0.73	0.17 ± 0.41	0.45 ± 0.47	0.15 ± 0.49	0.19 ± 0.41	−0.03 ± 0.38	0.13 ± 0.67
In-segment binary restenosis	27 (19)	15 (11)	6 (8.7)	13 (19.1)	19 (18.1)	24 (20.9)	8 (19.5)	2 (5.6)	NA	NA
Target lesion revascularization	12M: 20 (13.0)[e] 36M: 24 (15.6)[e]	12M: 7 (4.5)[e] 36M: 11 (7.1)[e]	12M: 5 (7.4) 36M: 8 (12.9)	12M: 11 (16.2) 36M: 14 (22.2)	12M: 11 (8.1)	12M:7 (5.0)	12M: 5 (5.8)	12M: 1 (1.2)	12M: 18 (12.5) 18M: 19 (13.5)	12M: 7 (10.1) 18M: 8 (11.6)
Target lesion thrombosis	12M: 3 (1.9) 36M: 4 (2.6)	12M: 2 (1.3) 36M: 2 (1.3)	12M: 1 (1.5) 36M: 2 (2.9)	12M: 0 36M: 0	12M: 0	12M: 0	12M: 0	12M: 0	12M: 1 (0.7) 18M: 1 (0.7)	12M: 2 (2.9) 36M: 2 (2.9)
MACE[f]	12M: 24 (16.0)[e] 36M: 38 (24.7)	12M: 10 (7.0)[e] 36M: 24 (15.5)[e]	12M: 7 (10.3) 36M: 13 (19.1)	12M: 13 (19.1) 36M: 20 (29.4)	12M: 15 (10.9)	12M: 13 (9.2)	12M: 6 (7.0)	12M: 4 (4-7)	12M: 25 (16.9) 18M: 26 (17.9)	12M: 10 (14.3) 18M: 13 (18.6)
Dual antiplatelet therapy, mo	3	12	≥6	≥6	12	12	≥6	≥6	NA	NA
Main conclusion	DES was angiographically and clinically more effective than DCB angioplasty		DCB was associated with noninferior angiographic effectiveness compared with DES implantation		DCB angioplasty was associated with noninferior angiographic effectiveness compared with DES implantation		DES was associated with superior angiographic effectiveness compared with DCB		DCB was associated with noninferior angiographic effectiveness compared with DES implantation	

Late lumen loss and percentage diameter stenosis are means and standard deviations. Binary restenosis and clinical outcomes are counts and rates.
BMS, bare-metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; MACE, major adverse cardiac events; NA, not available.

[a] Only DCB and DES arms are reported. The ISAR-DESIRE 3 was a 3-arm trial also including 134 patients randomly assigned to plain balloon angioplasty. [b] Patients analyzed at the clinical follow-up/lesions analyzed at the angiographic follow-up. [c] As assessed by optical coherence tomography. [d] Registration in ClinicalTrials.gov except for the DARE trial that was registered with the Netherland trials registry. [e] Significant differences. [f] RIBS IV: all-cause death, myocardial infarction, or target lesion revascularization; ISAR-DESIRE 3: all-cause death, myocardial infarction, or target lesion revascularization; PEPCAD China ISR: all-cause death, myocardial infarction, or any revascularization; RIBS V: all-cause death, myocardial infarction, or target vessel revascularization; SEDUCE: cardiac death, myocardial infarction, or target lesion revascularization, RIBS V: all-cause death, myocardial infarction, or target lesion revascularization; TIS: cardiovascular death, myocardial infarction, or target vessel revascularization; DARE: all-cause death, target vessel-related myocardial infarction, or target vessel revascularization; RESTORE: all-cause death, myocardial infarction, or target lesion revascularization; BIOLUX-RCT= cardiac death, myocardial infarction, or target lesion revascularization.

BMS restenosis

In the pivotal randomized PACCOCATH-ISR (Treatment of In-Stent Restenosis by Paclitaxel Coated PTCA Balloons) trial, 52 patients with BMS-ISR were randomly assigned to angioplasty with either plain balloon or DCB.[105] The primary angiographic end point of 6-month in-segment late lumen loss was significantly lower in the DCB group (0.03 ± 0.48 mm vs 0.74 ± 0.86 mm; $P = .002$).[105] The rates of 6-month binary restenosis (5% vs 43%; $P = .002$) and 12-month MACEs (4% vs 31%; $P = .01$) were consistently lower in the DCB arm.[105] After more than 5 years since index revascularization, the superior antirestenotic effectiveness of DCB over plain balloon angioplasty was confirmed.[106]

The PEPCAD II (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease II) trial showed that in 131 patients with BMS-ISR, DCB was associated with a significant reduction in the primary end point of 6-month late lumen loss compared with first-generation paclitaxel-eluting stents (0.17 ± 0.42 mm vs 0.38 ± 0.61 mm; $P = .03$).[101] No significant differences in the 6-month minimal lumen diameter and percentage diameter stenosis and the 12-month TLR (6.3% vs 15.4%; $P = .15$) were observed between DCBs and paclitaxel-eluting stents.[101] Of note, at the 3-year follow-up, no additional TLR occurred, and there were no significant differences between the treatment groups.[107]

More recently, the TIS (Treatment of In-Stent Restenosis) trial provided consistent results by comparing paclitaxel-coated balloon versus second-generation everolimus-eluting stent in 136 patients with BMS-ISR.[108] At 12-month angiography, patients treated by DCB showed a lower in-segment late lumen loss (0.02 vs 0.19 mm; $P = .0004$) and numerically lower binary restenosis (8.7% vs 19.1%; $P = .078$).[108] At the 3-year follow-up, results were unchanged, and no safety concerns emerged in the DCB and DES groups with comparable rates of MACEs (19.1% vs 29.4%; $P = .230$).[109] By contrast, the RIBS V trial including 189 patients with BMS-ISR randomized to DCB or everolimus-eluting stent showed that the primary end point of 6-month minimal lumen diameter was significantly lower after DES implantation than that after DCB angioplasty (2.36 ± 0.6 mm vs 2.01 ± 0.6 mm; $P < .001$).[110] However, except for a significant reduction in TLR associated with everolimus-eluting stent compared with that with DCB angioplasty (7.1% vs 15.6%; $P = .015$), at the 3-year follow-up, no significant differences in cardiac death (3.2% vs 3.9%; $P = .78$), myocardial infarction (4.5% vs 2.6%; $P = .25$), and definite or probable stent thrombosis (2.6 vs 1.3%; $P = .40$) were observed between the groups.[111]

DES restenosis

An early Japanese single-center trial of 50 patients with limus-DES-ISR demonstrated that DCB is associated with a lower angiographic late lumen loss (0.18 ± 0.45 mm vs 0.72 ± 0.55 mm; $P = .001$), which translated into a reduction in the rate of TLR (8.7% vs 62.5%; $P = .0001$).[112] These preliminary results were consistent with those of the larger PEPCAD-DES (Treatment of DES-ISR With SeQuent Please Paclitaxel Eluting PTCA Catheter) trial that confirmed in 110 patients with any-type DES-ISR that DCB angioplasty is significantly more effective than plain balloon angioplasty in both late lumen loss (0.43 ± 0.61 mm vs 1.03 ± 0.77 mm; $P < .001$) and TLR (15.3% vs 36.8%; $P = .005$), without late no catch-up at the 3-year follow-up.[100,113]

Later, the ISAR-DESIRE 3 (Randomized Trial of Paclitaxel-Eluting Balloon, Paclitaxel-Eluting Stent and Plain Balloon Angioplasty for Restenosis in "-Limus"-Eluting Coronary Stents) trials assessed the 3-group comparison: plain balloon vs paclitaxel-coated balloon vs paclitaxel-eluting stent, in patients with limus-DES-ISR, concluding that DCB was noninferior to DES ($P_{noninferiority} = .007$) regarding in-segment percentage diameter stenosis, and both these devices were superior to plain balloon (plain balloon, 54.1% ± 25.0% vs DCB, 37.4% ± 21.8% vs DES, 38.0% ± 21.5%; $P < .0001$ for DCB and DES vs plain balloon).[114] Incidences of TLR at 1 year across the plain balloon, DCB, and DES groups were consistent with an angiographic follow-up at 6-8 months (plain balloon, 43.5% vs DCB, 22.1% vs DES, 13.5%; $P < .0001$ for DCB and DES vs plain balloon). At the 3-year follow-up, no significant differences in TLR were observed.[115] In a subanalysis, no significant difference in postprocedural troponin levels among plain balloon, DCB, and DES was observed.[116] The results of the 10-year follow-up final analysis of the ISAR-DESIRE 3 trial showed that the composite end point of all-cause death, myocardial infarction, target lesion thrombosis, or TLR was significantly less frequent in the DCB and DES groups compared with the plain balloon group (plain balloon, 72.0% vs DCB, 55.9% vs DES, 62.4%; $P < .001$) (Figure 2), mainly because of a lower incidence of TLR, whereas no significant difference was observed between the DCB and DES groups (multiplicity-adjusted $P = .610$; weighted Cox HR, 1.10; 95% CI, 0.80-1.51; Cox HR, 1.10; 95% CI, 0.79-1.52; Royston-Parmar HR, 1.08; 95% CI, 0.72-1.62).[117] TLR was significantly lower in the DCB and DES groups compared with the plain balloon group (plain balloon, 58.0% vs DCB, 43.9% vs DES, 38.6%; $P < .0001$), without a significant difference between the DCB and DES groups (multiplicity-adjusted $P = .282$; weighted Cox HR, 0.83; 95% CI, 0.56-1.22; Cox HR, 0.81; 95% CI,

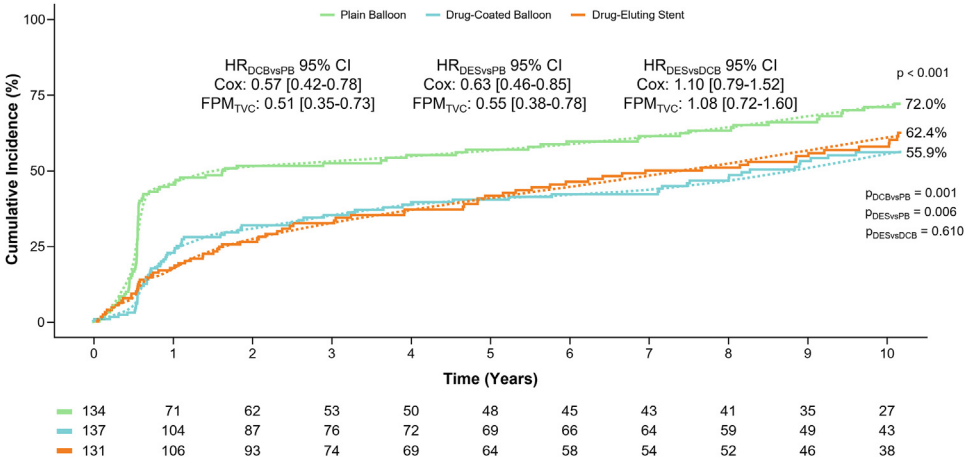


Figure 2.
Kaplan-Meier estimates of the device-oriented primary composite end point (cardiac death, target vessel myocardial infarction, target lesion thrombosis, or target lesion revascularization) of the ISRA DESIRE 3 trial.[117] DCB, drug-coated balloon; DES, drug-eluting stent; PB, plain balloon.

0.54-1.21; Royston-Parmar HR, 0.75; 95% CI, 0.47-1.20).[117] At the 10-year follow-up, numerical excess in death and cardiac death associated with DES compared with that with DCB was observed.[117] At landmark analyses, death and cardiac death within the first 5 years after percutaneous coronary intervention were significantly more frequent in the DES group than that in the DCB group (death, multiplicity-adjusted $P = .028$; cardiac death, multiplicity-adjusted $P = .047$).[117] Competing risk regression confirmed a nonsignificant difference in TLR between the DCB and DES groups and showed an increased risk of death associated with DES than that with DCB in patients without a preceding TLR.[117]

Similar results were observed in a randomized clinical study conducted in China comparing paclitaxel-coated balloon with paclitaxel-eluting stent in 220 patients with DES-ISR.[118] DCB and DES were associated with comparable 9-month late lumen loss (0.46 ± 0.51 mm vs 0.55 ± 0.61 mm; $P = .32$) and 2-year TLR (15.9% vs 13.7%; $P = .66$). In this trial, DES was associated with a higher incidence of death or myocardial infarction compared with DCB (3.7% vs 11.8%; $P = .03$), although the statistical power was insufficient to explore clinical end points.[119]

More recent trials of patients with DES-ISR tested DCB performance versus second-generation DES. In the RIBS IV (Restenosis Intra-stent of Drug-eluting Stents: Paclitaxel-eluting Balloon vs Everolimus-eluting Stent IV) trial, DCB was associated with inferior in-segment minimal lumen diameter (1.89 ± 0.7 mm vs 2.20 ± 0.7 mm; $P < .001$) and percentage diameter stenosis ($30\% \pm 22\%$ vs $23\% \pm 22\%$; $P < .001$) compared with everolimus-eluting stents.[120] At the 1-year clinical follow-up (16.0% vs 7.0%; $P = .009$) mainly because of a reduced need for TLR (13.0% vs 4.5%; $P = .007$).[120] These results were confirmed at the 3-year follow-up where TLR remained significantly higher in the DCB group than that in the DES group (15.6% vs 7.1%; $P = .015$).[48]

Mixed in-stent restenosis

The DARE (Drug-Eluting Balloon for In-Stent Restenosis) and BIOLUX-RCT (Clinical Performance of the Pantera Lux Balloon Versus the Orsiro Stent in Patients With In-stent Restenosis) trials, including both patients with BMS-ISR and DES-ISR reported similar effectiveness between DCB and second-generation DES, showed that DCB was noninferior to DES in primary angiographic end point—the 6-month minimum lumen diameter and late lumen loss, respectively—and there were no significant differences in clinical end points.[49,50] Observational studies provided mixed results, with some showing reduced revascularizations after DES implantation over DCB angioplasty and others reporting comparable antirestenotic efficacy.[121,122] However, in general, there were no differences across these studies in major safety end points.[121,122]

A few studies compared the performance of DCBs in patients with BMS or DES-ISR. In a small trial comparing 2 paclitaxel-DCBs with different excipients showed than the acetyl tri-butyl citrate-based DCB was noninferior to the iopromide-based DCB in the in-segment late lumen loss (0.40 ± 0.43 mm vs 0.39 ± 0.54 mm; $P_{noninferiority} = .046$). At 12 months, no significant differences were observed in TLR (7.7% vs 10.0%; $P = .89$) and major safety end points.

The DAEDALUS study

The DAEDALUS (Difference in Anti-restenotic Effectiveness of Drug-eluting stent and DCB AngiopLasty for the occUrrence of coronary in-Stent restenosis) study was a comprehensive, investigator-initiated, collaborative, individual patient data meta-analysis including all 10 available (n = 1976) randomized clinical trials comparing DCB angioplasty (n = 1033) with repeat stenting with DES (n = 943) for the treatment of coronary ISR.[123,124] At 3 years, DCB was associated with a moderate increase in the risk of TLR compared with DES (HR, 1.32; 95% CI, 1.02-1.70; $P = .035$).[123] There was a significant interaction between treatment effect and lesion-level type of restenosed stent ($P = .029$), with a more marked difference in patients with DES-ISR (HR, 1.60; 95% CI, 1.19-2.14; $P = .002$) and a comparable effect between treatments in patients with BMS-ISR (HR, 0.84; 95% CI, 0.51-1.38; $P = .490$).[123] The safety end point of all-cause death, myocardial infarction, or target lesion thrombosis was not significantly different between the groups (HR, 0.80; 95% CI, 0.58-1.09; $P = .152$).[123] However, a prespecified subgroup analysis indicated a significant interaction between treatment effect and generation of DES used to treat ISR in the composite safety end point ($P = .033$), with a lower incidence of events associated with paclitaxel-coated balloon than those with first-generation DES (HR,

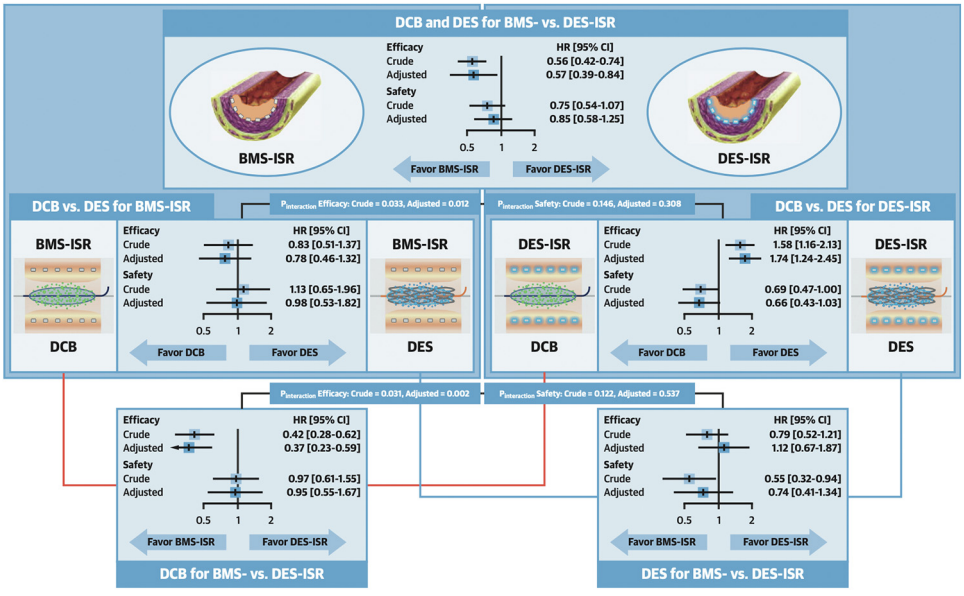


Figure 3.
Primary efficacy and safety end point risk of the DAEDALUS patient-level meta-analysis in clinical trials comparing DCB and DES in in-stent restenosis (ISR).[124] BMS, bare-metal stent; DCB, drug-coated balloon; DES, drug-eluting stent.

0.53; 95% CI, 0.32-0.87; $P = .012$) and a similar effect between paclitaxel-coated balloon and second-generation DES (HR, 1.06; 95% CI, 0.71-1.60; $P = .764$).[123]

The specific extensive patient-level analysis on ISR type (Figure 3) supported the very similar efficacy and safety of DCB and DES in the treatment of BMS-ISR.[124] In light of these results, DCB may be the preferred treatment strategy for BMS-ISR. By contrast, repeat DES implantation was moderately more effective than DCB angioplasty in the treatment of DES-ISR.[124] However, this result occurred at the cost of a numerical excess in the composite end point of all-cause death, myocardial infarction, or target lesion thrombosis with unclear interpretation against the known limitations in the statistical power of subgroup analyses.[124] The different efficacy of DCB between BMS-ISR and DES-ISR may partially rely on differences in the individual susceptibility to antiproliferative drug–mediated suppression of neointimal growth and neoatherosclerosis. Indeed, a proportion of DES-ISR lesions may be related to the failure of the antiproliferative drug eluted after implantation, whereas many BMS-ISR lesions may be still susceptible to the effects.[124] DCB is essentially a carrier for an antiproliferative medication and may more frequently encounter lower responsiveness in DES-ISR.[124] By contrast, although this limitation would also affect DES performance, repeat DES implantation may be more effective, at least in the first period, due to vessel scaffolding.[124] Another possible explanation may be adduced to neoatherosclerosis, which is known to occur earlier and more frequently in DES-ISR than that in BMS-ISR.[124] Neoatherosclerosis can present as tight fibrocalcific lesions that can substantially take advantage of the mechanical support of repeat DES implantation, whereas DCB may require more careful lesion preparation.[124]

In aggregate, the DAEDALUS study added new important insights on the topic, but a large contemporary trial designed to inspect efficacy and safety clinical end points at a long-term follow-up is still needed.

Combined treatments with DCB

Some studies have tested the use of devices in combination to DCB with the objective of improving treatment efficacy. In the ISAR-DESIRE 4 multicenter trial, patients with limus- eluting stent–ISR were randomly assigned to standard DCB angioplasty versus scoring balloon predilation, followed by DCB angioplasty.[125] At the angiographic follow-up, pretreatment with scoring balloon, followed by DCB, was associated with an improved percentage diameter stenosis (35% ± 16.8% vs 40.4% ± 21.4%; $P = .047$) and binary restenosis rates (18.5% vs 32.0%; $P = .026$) compared with DCB alone.[125] Another trial conducted in Japan compared by optical coherence tomography imaging predilation with a nonslipping element balloon catheter provided with 3 longitudinal nylon elements with predilation with a high-pressure noncompliant balloon before DCB application for the treatment ISR.[126] At the 8-month invasive follow-up, in-segment late lumen loss was not significantly different between nonslipping element balloon and noncompliant balloon predilation (0.28 ± 0.45 mm vs 0.27 ± 0.38 mm; $P = .75$).[126]

Comparison between DCBs for the treatment of ISR

Some trials have focused on the comparison between DCBs. Two paclitaxel-coated balloons with different excipients were compared in a randomized clinical trials of 240 patients conducted in China.[127] In this trial, a shellac-ammonium salt-based DCB was noninferior to an iopromide-based DCB regarding in-segment late lumen loss (0.38 ± 0.50 mm vs 0.35 ± 0.47 mm; $P_{noninferiority} = .02$). The incidence of 12-month target lesion failure was not significantly different between the treatment groups (13.3% vs 12.6%; $P = .87$) and major clinical end points.[127]

Another smaller trial conducted in Germany showed that at the 6-month follow-up, an acetyl tri-butyl citrate–based paclitaxel-coated balloon was noninferior to an iopromide-based DCB regarding in-stent late lumen loss (0.40 ± 0.43 mm vs 0.39 ± 0.54 mm; $P_{noninferiority} = .046$).[128] At 12 months, there was no significant difference across clinical end points between the treatment groups.[128]

Effect of the quality of lesion preparation

TLR rate after ISR treatment with DCB depends critically on the result of lesion preparation. Among 166 ISR lesions treated with DCB, the cumulative TLR rate was significantly lower (20.3% vs 35.5% at 2 years; $P = .04$) when lesion preparation fulfilled the DCB Consensus criteria (residual stenosis <30% and absence of flow-limiting dissections).[129] The difference was even more pronounced in a study including 256 patients (309 lesions). After 2 years, TLR was only 8.3% if residual stenosis <20% was achieved by lesion preparation, and simultaneously, the DCB diameter was ~91% of the stent and the inflation time was >60 seconds. After only partial compliance with these quality parameters, the TLR rate was already more than doubled (19.2%), and with complete disregard, it was 66.7%.[130]

Coronary physiology and intravascular imaging

Coronary physiology and intravascular imaging guidance for percutaneous coronary interventions have been associated with improved outcomes compared with angiography alone.[131–135] Although the amount of evidence on coronary physiology and intravascular imaging techniques in percutaneous coronary intervention with DCBs is limited, available reports do not indicate different conclusions compared with DES. Regarding physiologic measurements, data already exist for fractional flow reserve and pressure gradient measurements, demonstrating their suitability in the context of DCB interventions.[47,136,137]

In the treatment of de novo lesions, when target coronary segments have not excessively limited reference vessel diameter and lesions are not distal, intravascular ultrasound and optical coherence tomography can improve the selection of lesions amenable to DCB angioplasty and the predictability of results.

In a study, serial optical coherence tomography performance has shown the morphologic changes of ISR lesions after DCB angioplasty.[138] Postprocedural dissections were observed through the segment treated by DCB angioplasty, mainly where ISR was more severe.[138] Of note, these dissections were not visible on angiographic images and were left untreated, with complete healing at the invasive follow-up. More importantly, intravascular imaging with intravascular ultrasound or optical coherence tomography can provide insights into the mechanisms underlying ISR.[32,139–142] The identification of lesion-specific contributing mechanical and histopathologic factors can influence the decision between DCB and DES for the treatment of ISR and lesion preparation requirements (eg, aggressive predilation with noncompliant balloons, cutting balloon, and high-pressure balloons) before DCB application.[32,125,139]

New technologies: limus-coated balloons

Comparisons between the first-generation paclitaxel-eluting and sirolimus-eluting stents have given rise to the doctrine that sirolimus and its analogs are the preferred drugs for local vascular therapy.[143] Direct comparisons of paclitaxel-eluting and sirolimus-eluting stents showed significantly higher TLR rates with Taxus within the first year.[143,144] Subsequent advances in DES technology, with the

development of thinner-strut platforms and bioresorbable-polymer or polymer-free mechanisms of drug elution, essentially occurred in devices eluting sirolimus or its analogs on the basis of a possible lower effectiveness and higher toxicity of paclitaxel in stent-based application according to some studies.[145–147]

For paclitaxel-coated balloons, it could be shown that with a suitable formulation, a therapeutically effective tissue concentration can be achieved up to 6 months after a short-term application.[15] Early preclinical attempts to deliver sirolimus and its analogs with the technology used for paclitaxel-coated balloon were unsuccessful owing to insufficient tissue uptake and shorter tissue retention of limus drugs compared with paclitaxel.[24,25] Indeed, relevant differences exist between different coatings despite the irreversible binding of paclitaxel.[20] Some additional challenges influence the local delivery of sirolimus-coated balloons compared with traditional paclitaxel-coated balloons, primarily the need for an efficient technology to transfer sirolimus into the vessel wall.[148] Both nano-encapsulated sirolimus through a porous balloon and phospholipid-encapsulated sirolimus nanocarriers through DCBs have resulted in a rapid decline in tissue levels.[149,150]

In a research project with different drug concentrations, additives and modifications of the crystal structure, a crystalline coating with 4-µg sirolimus/mm^2 balloon surface allowed for a high drug delivery and, simultaneously, sufficient tissue persistence of up to 50% after 4 weeks.[12] Although some sirolimus-coated balloons are commercially available in Europe, this specific sirolimus-DCB is so far the only technology for which published, peer reviewed, randomized, controlled clinical data are available. In an initial first-in-man randomized clinical trial of 50 patients with DES ISR, at 6 months, the in-segment late lumen loss was 0.21 ± 0.54 mm in the paclitaxel-coated balloon group versus 0.17 ± 0.55 mm in the sirolimus-coated balloon group ($P = .794$).[151] In an extended study population of 101 patients consisting of the initial first-in-man trial and an identical trial conducted in Germany and Switzerland, the late lumen loss (0.25 ± 0.57 mm vs 0.26 ± 0.60 mm) was similar between sirolimus-coated balloon and paclitaxel-coated balloon, meaning the same efficacy on neointimal proliferation.[22] In a parallel trial of 70 patients with coronary de novo lesions, sirolimus-coated balloon was noninferior to paclitaxel-coated balloon (0.10 ± 0.32 mm vs 0.01 ± 0.33 mm) regarding in-segment late lumen loss. In-segment late lumen enlargement was more frequent with paclitaxel-coated balloon than that with sirolimus-coated balloon (58% vs 32%; $P = .019$).[23]

Another commercially available sirolimus-coated balloon is based on a nanocarrier technology of sirolimus encapsulated in a phospholipid bilayer.[150] However, clinical evidence on this device essentially relies in mixed-quality single-arm registries.[152,153] In a propensity score-matched comparison between a nanocarrier-based sirolimus--coated balloon and a paclitaxel-coated balloon, no significant differences in 12-month clinical outcomes were reported between the groups.[154] The ongoing TRANSFORM II trial will provide data on this sirolimus-coated balloon in 1325 patients with de novo coronary artery disease randomly assigned to sirolimus-coated balloon or everolimus-eluting stent treatment.[155]

Other sirolimus-coated balloons have been developed and may become available for clinical use in the future. Among these devices, a sirolimus-coated balloon is based on microreservoirs consisting of a biodegradable polymer poly(lactic-co-glycolic acid), and sirolimus coated with a phospholipid blend (amphipathic membrane) is currently tested in a large randomized clinical trial (SELUTION de novo, NCT04859985) of 3326 comparing this sirolimus-coated balloon with contemporary DES for the treatment of de novo coronary artery disease. Another sirolimus-coated balloon based on a balloon catheter with uniform-density laser-drilled micropores to deliver sirolimus encapsulated in biodegradable polyester–based polymers submicron particles during balloon inflation was tested in a first-in-man study of 50 patients with ISR.[149,156]

Finally, a biolimus-coated balloon has recently shown superior 9-month angiographic late lumen loss (0.16 ± 0.29 mm vs 0.30 ± 0.35 mm; $P = .001$) and late lumen enlargement (29.7% vs 9.8%; $P = .007$) compared with plain balloon in the treatment of small-vessel disease.[26] Further data on this type of DCB compared with a paclitaxel-coated balloon in the setting of ISR will be provided by the ongoing REFORM trial (NCT04079192).

Antiproliferative drug toxicity and long-term mortality

Paclitaxel and sirolimus show a different dose-response relationship for apoptosis and parameters describing cytotoxicity, histopathologic changes, and cytotoxicity parameters.[35,146,157] From this, some authors derive the thesis that sirolimus is essentially cytostatic and paclitaxel is also cytotoxic.[35,146,157] However, increased apoptosis and histopathologic changes were observed only at high paclitaxel concentrations,[35,146,157] which are typically found nearby the stent struts in the case of DES.[158]

By contrast, paclitaxel-coated balloons lead to a very uniform distribution of the drug in the vessel wall.[40] Typical paclitaxel concentrations for the treatment of femoropopliteal disease were well below those at which cytotoxic effects are observed. Regardless of the paclitaxel concentration on the balloon surface, ranging from 2 to 3 µg/mm^2, tissue levels of approximately 50-60 ng/mg occurred in the first hours after application, 5-20 ng/mg after 1 day, 2-10 ng/mg after 1 week, and further decreasing thereafter until disappearance after 30-45 days.[20]

The therapeutic window of a drug is usually defined as the range of drug dosages that can treat a disease effectively without having toxic effects. To evaluate the therapeutic window of DCBs, it makes sense to look at the systemic dose of the respective drug. Paclitaxel is commonly used for cancer treatment with a single dose of 100-175 mg/m^2 intravenous per treatment cycle; thus, a typical systemic dose is ~300 mg.[159] A coronary paclitaxel-coated balloon of 3.0 × 20 mm and 3 µg/mm^2 concentration of paclitaxel on the surface is coated with approximately 0.4 mg of antiproliferative drug, corresponding to a ratio of 750 between the systemic dose and the amount of drug required for the local treatment of coronary artery disease. In the case of peripheral artery disease, this ratio is 1 to 55 because required paclitaxel-coated balloons are significantly longer than those used for coronary artery disease (Table 3).

For sirolimus, a daily dose of 2 mg was administered orally for testing the effects on restenosis prevention. The dose of 5 mg, which was also studied, resulted in relevant side effects in the majority of patients.[160] Depending on the sirolimus concentration on the balloon, ranging from 1 to 4 µg/mm^2, the ratio for coronary arteries is only 1 to 3 and for peripheral arteries only 1 to 10. Beyond these limits, sirolimus-DCB reaches systemically effective doses. Therefore, the

Table 3. Comparison of paclitaxel and sirolimus dose in systemic with that in DCB treatment.

	Paclitaxel	Sirolimus
Systemic treatment	~300.0 mg Single dose of 100-175 mg/m^2 intravenously per cancer treatment cycle[159]	2.0 mg Daily oral dose for restenosis prevention, 5 mg not tolerated (67% side effects)[160]
DCB treatment	0.4 mg CAD Balloon 3.0/20 mm @ 3 µg/mm^2 5.5 mg PAD Balloon 5.0/80 mm @ 3.5 µg/mm^2	0.2-0.6 mg CAD Balloon 3.0/20 mm @ 1-4 µg/mm^2 1.6-6.4 mg PAD Balloon 5.0/80 mm @ 1-4 µg/mm^2

CAD, coronary artery disease; DCB, drug-coated balloon; PAD, peripheral artery disease.

assertion that sirolimus has a broader therapeutic window than paclitaxel is debatable (Table 3).

In the late 2018, a meta-analysis by Katsanos et al[161] raised concerns about a potential long-term mortality increase associated with paclitaxel-coated balloons for the treatment of peripheral artery disease compared with that of conventional balloons. The authors postulated that the excess in mortality was potentially related to late paclitaxel toxicity.[161] In response to this report, the United States Food and Drug Administration issued advisory letters, suggesting the avoidance of paclitaxel-coated balloons and strict surveillance of patients exposed to these devices until additional data were available.[162,163]

Subsequent patient-level analyses mitigated concerns about paclitaxel-coated balloon late toxicity, and no clear correlation between mortality and nominal paclitaxel dose was observed.[164–166] Indeed, in an analysis of 1649 patients treated with paclitaxel-coated balloons for femoropopliteal artery disease, no significant difference was observed in all-cause mortality across tertiles of nominal paclitaxel doses at crude and inverse probability of treatment weighting analyses.[164] However, an individual patient data meta-analysis of 8 trials with DCB for the treatment of femoropopliteal disease confirmed a 38% relative risk increase in 4-year mortality associated with paclitaxel-coated balloons (and a paclitaxel-eluting stent for a single trial) compared with that with conventional balloon, although a dose-response analysis confirmed the absence of association between paclitaxel and late mortality.[163] The limitations of performing post hoc analyses of trials can be be overcome by the large-scale, multicenter, randomized SWEDEPAD trial.[167] The results of the interim analysis showed in 2289 patients with lower limb diseases assigned to paclitaxel-based device (>95% DCBs) or uncoated devices that at a mean follow-up of 2.5 years, the risk of all-cause death was not significantly different between the groups (25.5% vs 24.6%; HR, 1.06; 95% CI, 0.92-1.22).[167] Although the results of the SWEDEPAD trial provide reassuring information, further analyses are needed.

Safety concerns associated with DCB angioplasty were not detected in the coronary artery disease setting.[124,168] In detail, in a meta-analysis comparing paclitaxel-coated balloons with other interventional devices for the treatment of coronary artery disease, long-term mortality was not significantly different between the groups.[168] Consistently, in the 10-year outcomes analysis of the ISAR-DESIRE 3 trial, the pairwise comparisons of paclitaxel-coated balloon and paclitaxel-eluting stent groups with the plain balloon group were not associated with an increased risk of death.[168]

Dual antiplatelet therapy requirements and HBR

The absence of randomized clinical trials particularly testing different antithrombotic therapy regimens after DCB angioplasty and the limited inclusion and the exclusion from randomized clinical trials testing different antithrombotic therapy durations after percutaneous coronary intervention of traditional settings of DCB angioplasty (eg, ISR) have led current European guidelines to recommend in patients without HBR a dual antiplatelet therapy duration of 6 months in stable coronary artery disease and 12 months in acute coronary syndrome.[169,170] However, for patients with HBR, a dual antiplatelet therapy duration of 3 months should be considered (class IIa), and a duration of 1 month may be considered (class IIb).[169] Currently, there is no specific recommendation in the United States because no DCB is approved for nonexperimental use in the coronary circulation.

However, several considerations support shorter dual antiplatelet therapy durations after stand-alone DCB angioplasty, and it is likely that dual antiplatelet therapy composition of $P2Y_{12}$ inhibitor has no influence on device-related thrombotic outcomes. Indeed, DCB technology avoids adding permanent metallic layers on coronary artery wall, which is one of the major thrombotic triggers, especially in the early period after implantation.[91,139] Observational data on DCBs for stable coronary artery disease have showed no signal of harm after a short dual antiplatelet therapy, and investigations on DCBs in patients with HBR highlighted a potential advantage of DCB angioplasty over DES implantation regarding antithrombotic therapy requirements.[89] The results of an observational study on 1025 patients treated with paclitaxel-coated balloon alone for coronary artery disease (de novo, 66.9%; BMS-ISR, 10.9%; DES-ISR, 22.6%) and receiving only 1 month of dual antiplatelet therapy showed low incidences of ischemic events at 9 months (cardiac death, 1.3%; myocardial infarction, 3.4%; target lesion thrombosis, 0.8%).[89]

Recently, the DEBUT (Drug-Eluting Balloon in Stable and Unstable Angina) trial showed in 220 patients with HBR undergoing percutaneous coronary intervention for de novo coronary artery disease that stand-alone DCB angioplasty was both noninferior and superior to BMS implantation for the 9-month cardiovascular death, nonfatal myocardial infarction, or ischemia-driven TLR (1% vs 14%; RR, 0.07; 95% CI, 0.01-0.52; $P_{\text{noninferiority}} < .0001$; $P_{\text{superiority}} = .0003$).[88] Of note, in this trial, patients received only 1 month of dual antiplatelet therapy, regardless of chronic or acute coronary syndrome, and no stent thrombosis occurred in the DCB arm.[88] On the basis of these findings, an expert consensus opinion indicated that empirical duration of dual platelet therapy of only 1 month should be sufficiently safe in preventing thrombotic complications after the DCB angioplasty.[91] Although several randomized clinical trials testing different dual antiplatelet durations after second-generation DES implantation reported favorable outcomes after 1-3 months of dual antiplatelet therapy, the minimal antithrombotic requirements after DCB angioplasty make this treatment strategy an appealing option in patients with HBR.[67,87,171]

Critical considerations

The European Society of Cardiology guidelines on myocardial revascularization currently recommend the use of DCBs only for the treatment of ISR, and there is no other indication with this type of device.[170] The discrepancy between these recommendations and contemporary clinical application of DCBs in Europe reflects the paucity of clinical trial results at the time of guideline development. In recent years, the amount of data on DCBs for the treatment of de novo disease has significantly improved.[55,57,59,63] However, the indications on large coronary arteries and bifurcation lesions are not yet well represented in randomized controlled trials.

Treatment of de novo lesions with DCB allows the avoidance of a permanent implant, which has been shown to be associated with a device-associated risk of long-term events.[172] Over the years, it has been shown that the potential benefits of DCB are achieved only when the focus of the procedure is on lesion preparation.[91] It follows that in diffuse coronary artery disease, DCB angioplasty can be considered as a treatment modality complementary to DES to reduce the number and length of stents. Segments showing acceptable results after lesion preparation can be treated by DCB angioplasty, whereas DES implantation can be limited to segments requiring a mechanical support. Education and training of the younger generation of interventional cardiologists is particularly needed to bring this hybrid approach into widespread clinical use.

Finally, DCBs for the treatment of coronary artery disease are not approved in the United States owing to the absence of a Food and Drug Administration–approved randomized clinical trial powered for clinical end points. However, accumulated clinical data on DCBs may eventually promote the conduction of randomized clinical trials in the United States in the next few years.

Declaration of competing interest

Bruno Scheller was named as coinventor on patent applications submitted by Charite Hospital in 2001 and 2002; he received lecture fees

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The research reported has adhered to the relevant ethical guidelines.

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