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Clinical applications of drug-coated balloon: what have we learned and where are we going?

Aplicações clínicas do balão farmacológico: o que aprendemos e aonde vamos?

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ABSTRACT – Since the introduction of coronary stents, in-stent restenosis has been one of the main stumbling blocks for its application in coronary artery disease. The drug-eluting stents have effectively reduced and become the mainstay of the interventional therapy of coronary artery disease. However, concerns of delayed stent thrombosis, dependency on prolonged dual antiplatelet therapy, and recurrent restenosis led to a quest for new treatment modalities that could address restenosis rates without drug-eluting-stent-related drawbacks. The drug-coated balloon has emerged as an additional tool in the armamentarium of interventional cardiology. It is usually a semicompliant balloon coated with antiproliferative agents encapsulated in a polymer matrix, which is released into the wall after inflation and contact with the intima, leaving no implant behind. This review highlights the rationale for drug-coated balloon use, its effectiveness in different clinical and lesion settings, and the future perspective.

Keywords: Drug-coated balloon; Percutaneous coronary intervention; In-stent coronary restenosis; Small vessel disease; Peripheral artery disease

RESUMO – Desde a introdução dos stents coronarianos, a reestenose intra-stent tem sido um dos principais obstáculos para sua aplicação na doença arterial coronária. Os stents farmacológicos efetivamente a reduziram e se tornaram a principal opção da terapia intervencionista na coronariopatia. No entanto, preocupações com trombose tardia do stent, dependência de terapia antiplaquetária dupla prolongada e reestenose recorrente levaram a uma busca por novas modalidades de tratamento, que pudessem abordar as taxas de reestenose sem as desvantagens relacionadas aos stents farmacológicos. O balão farmacológico surgiu como ferramenta adicional no arsenal da cardiologia intervencionista. Em geral, é um balão semicomplacente, revestido com agentes antiproliferativos encapsulados em uma matriz polimérica, que é liberada na parede após insuflação e em contato com a íntima, sem deixar implante. Esta revisão justifica o uso do balão farmacológico, sua efetividade em diferentes cenários clínicos e tipos de lesão, além das perspectivas para seu uso.

Descritores: Balão farmacológico; Intervenção coronária percutânea; Reestenose intra-stent; Doença em vasos de pequeno calibre; Doença arterial periférica

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INTRODUCTION

Percutaneous plain old balloon angioplasty (POBA) revolutionized coronary revascularization. However, the acknowledgement of the limitations of POBA, including vessel dissection, elastic recoil, constrictive remodeling, and intimal hyperplasia, led to the development of coronary stents. Although bare-metal stents (BMS) successfully addressed the acute complications of vessel dissection, as well as the problems of elastic recoil and constrictive remodeling, they did not impact on intimal hyperplasia and led to the creation of a new clinical problem – in-stent restenosis (ISR). The drug-eluting stents (DES) have dramatically improved the clinical outcomes of patients undergoing percutaneous coronary intervention (PCI) by reducing the risk of ISR and repeat revascularization. However, late stent thrombosis and recurrent restenosis, with a risk of nearly 2% per year after implantation,

remained a concern¹ and motivated the innovation of drug-coated balloons (DCB). The rationale of DCB technology was a combination therapy of balloon and drug to treat coronary lesions, eliminating stent thrombosis, and achieving lower rates of restenosis by leaving no implant behind.² Although their efficacy and safety have been proved for both ISR and native small-vessel disease, there are other emerging indications (e.g., bifurcation lesions, large-vessel disease, diffuse disease, high bleeding risk, acute coronary syndrome). This device not only fulfills the specific needs in the coronary vasculature, but also there is great potential for its use in other non-coronary vascular territories and structures including the management of valvar disease, congenital heart disease and neurovascular interventions.

MECHANISM OF ACTIONS OF DRUG-COATED BALLOONS

The initial extensive research to develop local delivery of drugs into the vessel wall was met with ungratifying clinical results, due to absorption variability and quick washout of drugs being studied. The interest in non-stent based local drug delivery system was rekindled with the emergence of sirolimus and paclitaxel, both lipophilic drugs absorbed rapidly by the arterial tissue. The key elements of DCB are balloon platform, drug, excipient, and balloon coating process. Once the balloon is inflated, acute drug transfer occurs almost immediately to deliver the drug from the balloon's surface to the arterial wall, mostly binding to hydrophobic binding sites on the latter, with lesser amount being transported by diffusion and convection.³⁻⁶ Factors impacting transfer efficiency include the inherent physicochemical properties of the drug, manufacturing and coating process, and the presence of excipients. Excipients increase drug transfer capability by counteracting the hydrophobicity of the drug which causes it to remain on the balloon surface. The antiproliferative drug applied to DCB has traditionally been paclitaxel, although recent DCB development is witnessing the use of limus-based drugs instead, due to cytotoxicity of paclitaxel.

Paclitaxel still remains the drug of choice, with a typical dose between 2ug/mm² and 3.5ug/mm² on the balloon surface. The coating formulation and the technique of the coating procedure enable successful drug transfer; thus resulting in different pharmacokinetic profiles.⁷ Therefore, the interaction among drug doses, formulations, release kinetics, and lesions seems to be crucial for the vascular response after DCB therapy. Of note, there is no evidence of a "class effect" among different platforms.⁸

DRUG-COATED BALLOON PLATFORMS

The balloon coating should ideally exhibit robustness to retain drugs on the surfaces as during tracking of the device while providing efficient and homogeneous drug transfer to vessel walls. Various excipients have been tested to deliver

the antiproliferative agent to the lesion site. Paclitaxel is loaded onto the balloon with spraying, dipping, nanoparticles and imprinting the drug on the rough surface of the device. Overall, most of the available DCB (Table 1) release the drug within the first hours/days after the procedure. To overcome the low lipophilicity and drug retention, novel drug carriers were recently developed, including nanoparticles, which encapsulate the limus-based drugs controlling their release at the lesion site.⁹

DRUG-COATED BALLOONS APPLICATION IN CORONARY ARTERY DISEASE

Although the efficacy and safety of DCB have been proved for both ISR and native small-vessel disease (SVD), there are other emerging indications (e.g., bifurcation lesions, large-vessel disease, and high bleeding risk).

In-stent restenosis

BMS ISR (characterized by neointimal hyperplasia) and DES ISR (characterized by neointimal hyperplasia with late neoatherosclerotic changes),¹⁰ both benefit from PCI with DCB (Table 2 and 3).¹¹⁻²⁵ DES ISR represents a complex scenario of high-risk population, with primary failure of local drug delivery by the stent.^{26,27} The potential relative efficacy of DCB *versus* DES, according to the underlying tissue substrate (e.g., neointimal hyperplasia *versus* neoatherosclerosis) may be different. All treatment strategies for coronary ISR lesions were reviewed in a meta-analysis by Siontis et al.,²⁸ and it was concluded that "two strategies should be considered for treatment of any type of coronary ISR: PCI with everolimus-eluting stents because of the best angiographic and clinical outcomes, and DCB because of its ability to provide favorable results without adding a new stent layer". Another meta-analysis demonstrates that DCB are similarly effective as DES in the reduction of revascularization for BMS ISR, whereas they have somewhat lower efficacy in DES ISR.²⁹ The desirability of deploying a DES compared to DCB is decreased due to new permanent metal layer. Therefore, many interventional cardiologists prefer to use DCB over DES in patients presenting with first ISR, reserving the use of another DES layer for patients with subsequent recurrences after DCB treatment. The use of DCB instead of repeat DES is particularly appealing in patients with multilayered ISR, in those with relevant side branches emerging from the stent with ISR, and in those who may benefit from a shorter dual-antiplatelet therapy (DAPT).³⁰ The European Society of Cardiology (ESC) guidelines has granted the use of DCB for the treatment of BMS or DES ISR (class I, level A).⁸ Intravascular imaging is highly recommended to detect "mechanical" causes of ISR and correct them accordingly.³⁰ However, the use of DCB in conventionally undilatable lesions should be avoided. Rotational atherectomy (RA),³¹ intravascular lithotripsy (IVL),³² and scoring or cutting balloons may be useful adjuncts to improve stent expansion and luminal gain, besides avoiding slippage of pre-dilation balloons.^{33,34}

Table 1. Drug-coated balloon devices available for percutaneous coronary intervention

Device	Company	Drug	Dose	Excipient
Agent	Boston Scientific	Paclitaxel	2ug/mm ²	Citrate ester
AngioSculptX	Spectranetics	Paclitaxel	3ug/mm ²	Nordihydroguaiaretic acid
BioStream	Biosensors International Group	Paclitaxel	3ug/mm ²	Shellac
Chocolate Touch	QT Vascular	Paclitaxel	3ug/mm ²	Undisclosed
DIOR I	Eurocor	Paclitaxel	3ug/mm ²	Shelloic acid
DIOR II	Eurocor	Paclitaxel	3ug/mm ²	Shelloic acid
Danubio	Minvasys	Paclitaxel	2.5ug/mm ²	Butyryl-tri-hexyl citrate
Elutax	Aachen Resonance, Aachen, Alemanha	Paclitaxel	2.2ug/mm ²	Dextrane
Essential	iVascular S.L.U.	Paclitaxel	3ug/mm ²	Organic ester
GENIE	Acrostak Corporation Winterthur	Nanoporous	10umol/L	None
IN.PACT Falcon	Medtronic, Santa Rosa	Paclitaxel	3ug/mm ²	Urea
MagicTouch Xtreme Touch™ DCB	Concept Medica	Sirolimus + nanocarriers	1.27µg/mm ² 3.00µg/mm ²	Phospholipid
Pantera Lux	Biotronik	Paclitaxel	3ug/mm ²	Butyryl-tri-hexyl citrate
Protégé & Protégé NC	Blue Medical	Paclitaxel	3ug/mm ²	Butyryl-tri-hexyl citrate
PACCOCATH	Bayer, Bavaria Medizin Technologie	Paclitaxel	3ug/mm ²	Iopromide
RESTORE®	Cardionovum	Paclitaxel	3ug/mm ²	Safepax
SELUTION	M.A. Med Alliance	Sirolimus nanoparticles	1ug/mm ²	Cell adherence technology
SeQuent® Please	B. Braun Melsungen AG	Paclitaxel	3ug/mm ²	Iopromide
SeQuent® Please SCB	B. Braun Melsungen AG	Sirolimus	4ug/mm ²	Crystalline sirolimus
Virtue	Caliber Therapeutics	Sirolimus nanoparticles	3mg	Porous balloon

Table 2. Summary of major randomized clinical trials of drug-coated balloons in bare-metal stents and mixed in-stent restenosis

Study (year)	Comparators to PCB	n	Follow-up duration	Angiographic follow-up (p-value)	MACE % (p-value)	TLR % (p-value)
PACCOCATH ISR I and II ^{11,12} (2006 and 2012)	POBA	108	6 months (angiographic) 12 months (clinical) 5 years (clinical)	LLL 0.03mm±0.48 versus 0.74mm±0.86 (0.0002)	4 versus 31 (0.01)	0 versus 23 (0.02)
PEPCAD II ¹³ (2009)	PES	131	6 months (angiographic) 12 months (clinical) 3 years (clinical)	LLL 0.17mm±0.42 versus 0.38mm±0.61 (0.03)	9 versus 22 (0.08)	6 versus 15 (0.15)
RIBS V ¹⁴ (2016)	EES	189	6-9 months (angiographic) 12 months (clinical) 3 years (clinical)	LLL 0.14mm±0.5 versus 0.04mm±0.5 (0.14), binary restenosis 9.5% versus 4.7% (0.22)	8 versus 6 (0.60)	6 versus 1 (0.001)
SEDUCE ¹⁵ (2014)	EES	50	9 months (angiographic) 12 months (clinical)	LLL 0.28mm versus 0.07mm (0.1) proportion uncovered struts (OCT) 1.4% versus 3.1% (0.025)		4.2 versus 8 (0.576)
TIS ¹⁶ (2016)	EES	136	12 months	LLL 0.02mm versus 0.19mm (0.0004)	10.3 versus 19.1 (0.213)	7.4 versus 16.2 (TVR) (0.110)
BIOLUX ¹⁷ (2018)	SES	229	6 months (angiographic) 12 months (clinical)	LLL 0.03mm±0.40 versus 0.20mm±0.70 (0.40)	16.9 versus 14.2 (TLF) (0.65)	12.5 versus 10.1 (0.82)
DARE ¹⁸ (2018)	EES	278	6 months (angiographic) 12 months (clinical)	MLD 1.71mm±0.51 versus 1.74mm±0.61 (<0.0001, non-inferiority)	10.9 versus 9.2 (0.66)	7.1 versus 8.8 (TVR) 7.1 versus 8.8 (TVR)

PCB: paclitaxel-coated balloon; MACE: major adverse cardiovascular events; TLR: target lesion revascularization; POBA: plain old balloon angioplasty; PES: paclitaxel-eluting stent; EES: everolimus-eluting stent; OCT: optical coherence tomography; MLD: mean luminal diameter; TLF: target lesion failure; TVR: target vessel revascularization.

Table 3. Summary of major randomized clinical trials of drug-coated balloon in drug-eluting stent in-stent restenosis

Study (year)	Comparators to PCB	n	Follow-up duration	Angiographic follow-up (p-value)	MACE % (p-value)	TLR % (p-value)
PEPCAD-DES ¹⁹ (2012)	POBA	110	6 months (angiographic and clinical) 3 years	LLL 0.43mm±0.61 <i>versus</i> 1.03mm±0.77 (<0.001), restenosis 17.2% <i>versus</i> 58.1% (0.001)	16.7 <i>versus</i> 50.0 (<0.001)	15.3 <i>versus</i> 36.8 (0.005)
PEPCAD China-ISR ²⁰ (2014)	PES	220	9 months (angiographic) 12 months (clinical) 2 years (clinical)	LLL 0.46mm±0.51 <i>versus</i> 0.55mm±0.61 (0.0005, noninferiority)	16.5 <i>versus</i> 16 TLF (0.92)	15.6 <i>versus</i> 12.3 (0.48)
ISAR-DESIRE-3 ²¹ (2013)	PES <i>versus</i> POBA	402	6-8 months (angiographic) 12 months (clinical) 3 years (clinical)	Diameter stenosis 38% <i>versus</i> 37.4% (0.007, non-inferiority)	23.5 <i>versus</i> 19.3 <i>versus</i> 46.2 (0.5 PCB <i>versus</i> PES)	22.1 <i>versus</i> 13.5 <i>versus</i> 43.5 (0.09 PCB <i>versus</i> PES)
ISAR DESIRE 4 ²² (2017)	Scoring and PCB	252	6-8 months (angiographic) 12 months (clinical)	LLL 0.31mm±59 <i>versus</i> 0.41±0.74mm (0.27)	18.4 <i>versus</i> 23.3 (0.35)	16.2 <i>versus</i> 21.8 (0.26)
RIBS IV ²³ (2015)	EES	309	6-9 months (angiographic) 12 months (clinical)	Binary restenosis 19% <i>versus</i> 11% (0.06)	18 <i>versus</i> 10 (0.04)	16 <i>versus</i> 8 (0.035)
RESTORE ²⁴ (2018)	EES	172	9 months (angiographic) 12 months (clinical)	LLL 0.15mm±0.49 <i>versus</i> 0.19mm±0.41 (0.54)	7.0 <i>versus</i> 4.7 (0.51)	5.8 <i>versus</i> 1.2 (0.10)
FIM LIMUS DCB ²⁵ (2019)	SCB	50	6 months (angiographic)	LLL 0.21mm±0.54 <i>versus</i> 0.17mm±0.55 (0.79)	16 <i>versus</i> 12 (>0.99)	16 <i>versus</i> 12 (>0.99)

PCB: paclitaxel-coated balloon; MACE: major adverse cardiovascular events; TLR: target lesion revascularization; POBA: plain old balloon angioplasty; PES, paclitaxel-eluting stent; EES: everolimus-eluting stent; SCB, sirolimus-coated balloon.

De novo coronary lesions

Despite extensive studies, the efficacy and safety result of DCB in *de novo* coronary lesions are conflicting. All these studies adopted two main approaches. In combination strategy, a BMS or DES was deployed after initial angioplasty with DCB; while in the “leave nothing behind strategy,” DCB angioplasty was performed, and a stent was implanted only as a bailout strategy for the suboptimal result after the DCB. Although a hybrid treatment of DCB and DES was advocated in patients at high risk for restenosis, such as those with diabetes, clinical data are lacking in this group.²

Small vessel disease

The interventional treatment of *de novo* small vessel disease (SVD), usually defined as lesions in vessels ≤2.75mm or <3.0mm, remains challenging due to the increased risk of adverse clinical outcomes, including higher rates of restenosis and thrombosis.³⁵ This may be due to limited ability of the vessel to adapt to neointima formation, which might develop after stent deployment.³⁶ DCB may be a potential advantage in this scenario due to less vessel inflammation in the absence of metallic stent layers, reducing abnormal flow and allowing positive vessel remodeling. The clinical feasibility of the treatment of SVD with DCB has initially been demonstrated in several nonrandomized studies and

registries.^{27,37-42} Subsequently, several randomized clinical trials were conducted that compared DCB with POBA,⁴³ BMS,⁴⁴ and DES (Table 4).⁴⁵⁻⁴⁸ In some studies, the lack of better efficacy of DCB *versus* POBA alone⁴³ was attributed to a very low event rate and of DCB *versus* DES⁴⁵ and the types of DCB used, in particular the excipient and rate of drug transfer, as well as an inadequate implantation and geographic mismatch.⁴⁹ However, larger and adequately designed trials showed similar results for DCB compared with the stents. BASKET-SMALL 2 (Basel Stent Kosten-Effektivitäts Trial Drug Eluting Balloons vs. Drug-Eluting Stents in Small Vessel Interventions)⁴⁷ is the largest study to date on SVD that compared a paclitaxel-iodipromide-coated DCB with second generation DES regarding clinical endpoints and demonstrated noninferiority of the DCB to the second generation DES. The study RESTORE SVD (Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease)⁴⁸ compared the RESTORE® DCB (Cardionovum, Bonn, Germany) with zotarolimus DES and demonstrated that DCB was noninferior to new-generation DES for the primary endpoint for stenosis percentage, and showed no significant clinical or angiographic differences in comparison with DES, at 12-month follow-up. Percutaneous coronary intervention

Table 4. Randomized controlled trials of drug-coated balloon only in treatment of *de novo* small vessel coronary artery disease

Study	Design	n	Follow-up duration	Angiographic follow-up (p-value)	MACE % (p-value)	TLR % (p-value)
PICCOLETO II ⁴⁵ (2010)	Dior PCB <i>versus</i> TAXUS Liberté™ SEP	57	6 months (angiography) 9 months (clinical)	MLD 1.11mm±0.65 <i>versus</i> 1.94mm±0.72 (0.0002)	35.7 <i>versus</i> 13.8 (0.054)	32.1 <i>versus</i> 10.3 (0.15)
BELLO ^{46,50,51} (2012)	IN.PACT Falcon PCB <i>versus</i> TAXUS Liberté™ SEP	182	6 months (angiography) 12 months (clinical) 3 years (clinical)	LLL 0.08mm±0.38 <i>versus</i> 0.29mm±0.44 (0.001)	10 <i>versus</i> 16.3 (0.21)	4.4 <i>versus</i> 7.6 (0.37)
RESTORE SVD ⁴⁸ (1918)	RESTORE® PCB <i>versus</i> Resolute Integrity SEZ	230	9-12 months (angiography) 12 months (clinical)	LLL 0.26mm±0.42 <i>versus</i> 0.30mm±0.35 (0.41) diameter stenosis 29.6%±2.0 <i>versus</i> 24.1%±2.0 (<0.001)	9.6 <i>versus</i> 9.6 (1.0)	4.4 <i>versus</i> 2.6 (0.72)
BASKET-SMALL 2 ⁴⁷ (2018)	Sequent Please PCB <i>versus</i> TAXUS Element SEP and Xience SEE	758	6 months (angiography) 12 months (clinical)	LLL 0.13mm (-0.14 to 0.57mm) <i>versus</i> 0.10mm (-0.16 to 0.34mm) 0.72	8 <i>versus</i> 8 (0.918)	3.4 <i>versus</i> 4.5 (0.438)

MACE: major adverse clinical events; TLR, target lesion revascularization; LLL: late lumen loss.

with the IN.PACT Falcon DCB (Medtronic-Invatec, Frauenfeld, Switzerland) showed lower late lumen loss (LLL) and similar rates of restenosis and revascularization as compared to the Taxus DES at 6 months in BELLO (Balloon Elution and Late Loss Optimization Study).⁴⁶ At 2-year follow-up of this study,⁵⁰ there was a trend toward lower clinical events in patients in the DCB group, and at 3-year follow-up,⁵¹ major adverse cardiovascular events (MACE) rates were significantly lower with DCB than with DES (14% *versus* 30%).

Large vessel disease

Drug-coated balloons-only strategy is found to be safe and effective in the treatment of *de novo* lesions in large (3.0-mm) coronary arteries as well with low risk rates of clinical events and acute vessel closure, which may be due to the lack of foreign material and its inherent thrombogenicity.^{40,41,44} However, further randomized controlled trials (RCT) comparing DCB with latest generation DES in this scenario are warranted.

Bifurcation lesions

Coronary bifurcation lesions are still a challenge for PCI due to unsatisfactory clinical outcomes, mostly in the side branch (SB). Even with DES, the risk of SB restenosis still remains high, particularly when more complex techniques are contemplated. There are currently 2 DCB strategies for the treatment of bifurcation lesions: DCB in SB and DES in main branch (MB); and DCB in both MB and SB. The ESC guidelines recommend MB stenting with provisional SB stenting as the default strategy.⁸ In this scenario, the DCB may be preferable to POBA in the SB. The PEPCAD (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) V

study employed a BMS in the MB in combination with a DCB in treatment in the SB and demonstrated a low LLL in the SB when treated alone with a DCB.⁵² Few observational studies focusing largely on a DES in the MB combined with a DCB in the SB strategy demonstrated good SB results.^{53,54} Drug-coated balloons-only PCI in bifurcation lesions with SB ≥2mm exhibited low rates of restenosis and target lesion revascularization (TLR),^{55,56} and this approach was superior for Medina class 0,1,1 lesions in a randomized trial, compared with POBA alone.^{57,58} A DCB-only PCI to the MB is often adequate and supported by the fact that ostial SB lesions may depict positive remodeling.⁵⁹ DCB compared with DES use in bifurcations allows simplification of the procedure, and the majority of work can be performed in a sequential manner. Kissing balloon angioplasty is feasible in selected cases, although carina shift normally is caused by stent implantation and not by balloon angioplasty.⁶⁰ However, a DES MB and DCB SB strategy may be selected in case of a compromised result during the pre-dilation stage of DCB-only PCI.

Acute coronary syndrome

The local delivery of drug by DCB is quite attractive in ST-segment elevation myocardial infarction (STEMI) patients while embarking on primary PCI, because it has potential advantage of preserving endothelial function, lowering risk of thrombosis due to less malapposition and homogeneous administration of the drug. Of note, a particular attention should be paid to the avoidance of DCB in the setting of high-grade thrombus, which may inhibit drug delivery to the vessel wall. Staging for PCI following restoration Thrombolysis in Myocardial Infarction (TIMI)

3 flow is also possible and may be particularly attractive for a DCB strategy.⁶¹ Only limited data exist for PCI with DCB on acute coronary syndrome.⁶²⁻⁶⁶ The study REVELATION (REVascularization With PaclitaxEL-Coated Balloon Angioplasty Versus Drug-Eluting Stenting in Acute Myocardial InfarcTION) compared DCB angioplasty with the Pantera Lux balloon (Biotronik AG, Bülach, Switzerland) with sirolimus or everolimus DES, and showed no significant difference in LLL and MACE at 9 month follow-up.⁶⁶ This study supports the hypothesis that DCB PCI may have a place in STEMI, where the lesions are generally short and less calcified and the patients typically younger for whom avoiding stent implantation may be a good idea. The DCB-only strategy is noninferior to stent treatment in non ST-segment elevation myocardial infarction (NSTEMI) as well.⁶²

Long and diffuse lesion

The hybrid approach of combining DCB with DES has been evaluated in long *de novo* lesions and diffuse coronary artery disease. This approach employs a DES implantation in the proximal lesion, and DCB in the distal lesion. This ensures an overall reduction in stent length, which in turn might be beneficial for lowering restenosis rates. However, it is important to note that these devices are not intended to treat the same diseased vessel segment. Of note, in the combination therapy approach for diffuse disease, the sequential lesions should be treated separately, and there should be no overlap between the treated segments because of a higher risk of restenosis. Costopoulos et al.⁶⁷ reported that this approach was acceptable, with comparable MACE and TLR rates in the treatment of diffuse coronary artery disease. An ongoing clinical trial, HYPER (Drug-Coated Balloon in Combination With New Generation Drug-Eluting Stent for *de Novo* Diffuse Disease Treatment; NCT03939468) may provide further insight.

High bleeding risk

Drug-coated balloons may be indicated in patients with a high risk of bleeding, patients on anticoagulation agents or undergoing recent surgery, such as those with atrial fibrillation. Although DAPT duration after PCI using DES has been shortened, antithrombotic agents may be stopped in case of life-threatening bleeding earlier after DCB than after DES. The recommended duration of DAPT is 4 weeks after a DCB-only strategy in *de novo* vessels, with favorable results in recent clinical trials for patients in stable condition.^{44,47} There are preliminary data that PCI using DCB may be performed using only one antiplatelet drug in case of exceptionally high bleeding risk.⁶⁸ The reported incidence of acute vessel thrombosis risk is only zero to 0.2% after DCB-only PCI in comparison with stent implantation.⁴⁰ Considering this, the duration of DAPT after DCB PCI might be shortened further in patients at high bleeding risk, and oral anticoagulation might be combined with a single antiplatelet agent in individual patients.

PERIPHERAL ARTERIAL DISEASE

Symptomatic peripheral artery disease is associated with significant morbidity and mortality. Several RCT have demonstrated that DCB and DES result in superior patency and decreased target lesion failure, when compared to standard, non-DCB (percutaneous transluminal angioplasty) and BMS for the treatment of femoropopliteal artery disease.⁶⁹⁻⁷² The performance of DCB for below-the-knee disease has been less conclusive.

OTHER NOVEL DEVELOPMENTS: WHERE ARE WE GOING?

In future, this technology is likely to find a place in the management of neurovascular, valvular, and pediatric congenital diseases. The ability to perform therapeutic dilatation followed by local drug delivery to prevent restenosis has generated interest in aortic valvuloplasty and in the treatment of basilar artery, subclavian vein, and arteriovenous hemodialysis fistula stenosis. The concept of drug-eluting valvuloplasty could also be theorized for mitral and pulmonary vein stenosis (Table 5).⁷³

DCB technology continues to evolve with improvements in excipient technology and introduction of sirolimus. Further RCT are needed to demonstrate if limus-based DCB is safer and more effective compared to limus-based DES. DCB-only PCI overcomes negative remodeling effects of POBA (vessel shrinkage) and stent (neointimal hyperplasia). Being hydrophilic in nature, paclitaxel stays in the arterial wall for prolonged periods and inhibits smooth muscle cell proliferation, and with the absence of a metallic implant, DCB leads to positive remodeling of the arterial

Table 5. Suggested future applications of drug-coated balloon

Coronary artery disease
ST-elevation myocardial infarction
Bifurcation
Long diffuse disease
Valvular heart disease
Aortic stenosis (poor candidate for surgical or percutaneous aortic valve replacement)
Mitral stenosis
Pediatric interventions
Pulmonary vein stenosis
Pulmonary artery stenosis/restenosis
Neurovascular interventions
Vertebral artery stenosis
Basilar artery stenosis
Carotid in-stent restenosis
Other vascular interventions
Central vein stenosis
Stenosis of arteriovenous fistula and grafts
Internal pudendal artery stenosis

wall. Although DCB clinical trials fail to demonstrate the effects of positive remodeling, the prospective intravascular ultrasound (IVUS) and optical coherence tomography (OCT) studies^{74,75} have shown a trend toward positive remodeling, with no aneurysm formation with the use of DCB. This mandates the long-term follow-up studies to clearly identify this possible benefit of DCB. The application of an antiproliferative drug on cutting or scoring balloons would combine the benefit of balloon based atherectomy and antiproliferative properties of DCB. A novel paclitaxel-coated scoring balloon has been developed and successfully used in a first-in-human randomized controlled trial.⁷⁶ The preliminary data of the first in-human study demonstrated the Chocolate Heart DCB (TriReme Medical, Pleasanton, California) incorporating nitinol-constraining structure (designed to provide fast deflation and uniform re-wrap) is both feasible and safe to use.⁷⁷

The application of DCB should be examined further in small vessels, or in mid and distal vessels, where distal stents may be a disadvantageous for future coronary artery bypass grafting. These studies should be randomized 1:1 to the latest generation DES, with the primary endpoint of target lesion failure (TLF). Diabetic individuals often present with higher TLR, even with the latest generation DES, and could be another subset of patients. The patients enrolled should be followed up for at least 5 years, and given optimal medical therapy during follow-up.² The steps (Figure 1)

SC: semi-compliant; NC: noncompliant; CB: cutting balloon; SB: scoring balloon; B/A: balloon/artery; RA: rotational atherectomy; IVL: intravascular lithotripsy; HCCL: heavily calcified coronary lesion; IVUS: intravascular ultrasound; OCT: optical coherence tomography; ISR: in-stent restenosis; TIMI: Thrombolysis in Myocardial Infarction; DCB: drug-coated balloon; FFR: fractional flow reserve; DES: drug-eluting stent.

Figure 1. Tips and tricks of drug-coated balloon use.

must include an adequate lesion preparation with semi- or noncompliant (cutting or scoring balloon, RA or IVL for calcified lesions) with balloon artery ratio of 1:1; DCB diameter of 0.8x to 1x nominal vessel size, to avoid the mechanical complications from POBA; bailout stenting in cases of fractional flow reserve ≤ 0.80 , residual stenosis $>30\%$ or type C coronary dissections; and a thorough evaluation of elastic recoil by performing another angiogram, 10 to 15 min after initial angioplasty. If there is any significant reduction in lumen diameter, IVUS or OCT guided implantation of latest generation DES should be contemplated.²

CONCLUSION

Drug-coated balloon represents a new revolution as an important tool in the field of percutaneous coronary intervention. The initial enthusiasm of this technology has been hampered at the beginning of its introduction by several biases, due to anecdotal case reports, non-randomized small studies, and a lack of preclinical testing. Currently, drug-coated balloon is considered feasible, safe, and effective which has been validated in several studies with more in progress. The efficacy of drug-coated balloon is now proven, especially for in-stent restenosis and small-vessel disease with a good safety profile. The treatment of *de novo* bifurcations lesions, diffuse lesions, acute coronary syndrome and pediatric interventions, and valvular diseases are promising indications, but still need to be proven in large randomized trials. There is still much to learn about the mechanisms and outcomes of the use of this novel technology. Nevertheless, in a short time span, drug-coated balloon has demonstrated the capacity to have a significant impact on the practice of percutaneous cardiovascular intervention.

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CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: DD, RM, SR, NA and SAM; data collection: RR and RM; data interpretation: DD and NA; text writing: DD and SR; approval of the final version to be published: DD and SAM.

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